Immunology & Cell Biology 2024; **102**: 167–178
www.wileyonlinelibrary.com/journal/icb

REVIEW

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Extracellular vimentin as a modulator of the immune response and an important player during infectious diseases

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Keywords
Extracellular vimentin, host–pathogen interactions, immune modulation

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Received 23 September 2023;
Revised 27 November and 21 December 2023;
Accepted 21 December 2023

doi: 10.1111/imcb.12721

Immunology & Cell Biology 2024; **102**: 167–178

Abstract

Vimentin, an intermediate filament protein primarily recognized for its intracellular role in maintaining cellular structure, has recently garnered increased attention and emerged as a pivotal extracellular player in immune regulation and host–pathogen interactions. While the functions of extracellular vimentin were initially overshadowed by its cytoskeletal role, accumulating evidence now highlights its significance in diverse physiological and pathological events. This review explores the multifaceted role of extracellular vimentin in modulating immune responses and orchestrating interactions between host cells and pathogens. It delves into the mechanisms underlying vimentin's release into the extracellular milieu, elucidating its unconventional secretion pathways and identifying critical molecular triggers. In addition, the future perspectives of using extracellular vimentin in diagnostics and as a target protein in the treatment of diseases are discussed.

INTRODUCTION

Immune responses, crucial for protecting the host from infectious diseases, come into play when a pathogen—a virus, bacterium, fungus or parasite—enters the body.[1] The immune system typically recognizes the pathogen as foreign and initiates a response to neutralize and eliminate the threat.[2] Recent studies have highlighted the growing interest in the extracellular form of vimentin (eVim) in the context of immunomodulation, specifically within the intricate series of events during host–pathogen interactions.

eVim was initially identified in 2003 by Mor-Vaknin *et al.*,[3] marking a surprising revelation in the field. This discovery demonstrated that vimentin could be secreted, traverse onto the cell surface and influence the immune response of human macrophages.[3] The existence of eVim, whether in a free form in the bloodstream or bound to the cell surface, raises intriguing questions regarding its potential regulatory functions.[4,5] Indeed, recent findings have linked the presence of vimentin in the extracellular compartment or on the plasma membrane surface facing the extracellular space with various biological processes, including immune responses, cell signaling and tissue repair. These processes may unfold as a consequence of host–pathogen interactions, highlighting the involvement of eVim in the regulation of infection, inflammation and microorganism pathogenicity. Understanding the intricate interplay between eVim and pathogens could pave the way for new therapeutic interventions and diagnostic strategies. Furthermore, questions arise about the spatial arrangement of eVim, its length and post-translational

modifications, all of which can significantly impact the tertiary and quaternary structure of the protein and, consequently, its function.

This review delves into the immunomodulatory role of eVim, considering its demonstrated impact on diverse immune cell populations, including macrophages, neutrophils and lymphocytes.[6–8] Through its ability to regulate cytokine production, cell migration and phagocytic activities, eVim emerges as a critical mediator in inflammatory responses and immune surveillance.[9–11] In addition, we scrutinize the intricate interplay between eVim and pathogenic microorganisms. Recent studies have unveiled vimentin's role in microbial adhesion, invasion and dissemination.[12,13] The implications of these interactions on disease progression, immune evasion and potential therapeutic interventions are thoroughly discussed. Furthermore, the review explores the clinical relevance of eVim, particularly its diagnostic and prognostic potential as a biomarker for various inflammatory disorders and infectious diseases. The examination of vimentin-based therapeutic strategies, such as neutralizing antibodies or targeted protein inhibition, unveils new avenues for the development of novel immunomodulatory treatments.

EXTRACELLULAR VIMENTIN—IN THE SHADOW OF ITS FILAMENTOUS SIBLING

Distinct functions of extracellular vimentin connected to its physicochemical properties

Vimentin, both intracellular and extracellular, manifests as two distinct facets within the cellular microenvironment. Intracellularly, vimentin forms a dynamic cytoskeletal network, contributing significantly to cell shape, motility and organelle positioning.[14] By contrast, eVim has garnered increasing attention for its involvement in tissue homeostasis, inflammation and various pathological conditions. Released into the extracellular milieu through mechanisms including cell death or active secretion, eVim serves as a damage-associated molecular pattern molecule. Moreover, it plays a crucial role in immune modulation and tissue repair. The ability to distinguish between intracellular vimentin and eVim is paramount in comprehending its multifaceted functions and evaluating its potential as a therapeutic target across various diseases, rendering it a subject of intense research scrutiny.

Intracellular vimentin and eVim share similar molecular masses, hovering at approximately 54 kDa.[4,15] However, their apparent sizes exhibit significant disparities. Intracellular vimentin filaments, with an axial repeat of approximately 49 nm, show consistency in both cellular and *in vitro* settings. Unit-length filaments, the fundamental building blocks of vimentin filaments, exhibit a measurement of about 59 nm, indicating a partial overlap during the filament assembly process.[16]

By contrast, the hydrodynamic diameter of eVim, reflecting the extracellular environment, ranges from 5 (monomer) to 12 nm (octamer) according to the Stokes–Einstein formula, as estimated by Wasilewska *et al.*[17] On the mica surface, mimicking cell surface vimentin, the aggregate size was determined to be 12 ± 2 nm using atomic force microscopy. The study by Carse *et al.*[18] suggested that eVim adopts a globular rather than a filamentous form. The size variation between intracellular vimentin and eVim likely stems from their distinct cellular contexts, influencing electrostatic charge, quaternary structure and accessibility of potential functional sites.

Furthermore, the length variation of eVim can be attributed to proteases in the extracellular environment during inflammatory secretion by neutrophils or macrophages. These enzymes, including neutrophil elastase, myeloperoxidase and leukocyte proteinase 3, contribute to extracellular traps formation and may potentially cleave vimentin in the extracellular environment.[19–21] In intracellular environments, proteases such as calpains cleave filamentous vimentin during pyroptosis and cell migration processes, increasing vimentin solubility.[22–24] Caspase-3 and Caspase-7 disrupt vimentin filaments at Asp85, while Caspase-6 at Asp259 generates a proapoptotic amino-terminal fragment.[25] Matrix metalloproteinase-25 has been reported to cleave vimentin, influencing migration and invasion.[26]

In addition, the diverse functions of vimentin depending on its cellular localization can be attributed to the influence of ions and ionic strength. These factors significantly impact vimentin's behavior, including stability, interactions with other proteins, ligand-binding ability and solubility. In essence, ionic conditions in the extracellular milieu play a pivotal role in shaping vimentin's functional outcomes.[18,27]

Conditions and stimuli that lead to extracellular vimentin presence

Elevated blood levels of eVim have been observed in patients with pulmonary lung fibrosis, sepsis, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and coagulopathy.[4,28–30] During inflammation, endothelial cells and immune cells, such as neutrophils and macrophages, may release vimentin as part of their immune response.[12,31,32] In addition, when cells undergo injury or necrosis, their contents, including vimentin, can be passively released into the extracellular space as a result of physical trauma, chemical exposure or ischemic damage.[32,33]

Notably, eVim may play a significant role in tumor progression, invasion and metastasis. In certain cancer types, such as glioblastoma, breast, lung, gastric, liver and pancreatic cancer, tumor cells may actively release vimentin into the extracellular space.[34–39] This dual role

of eVim in both passive and active release underscores its potential impact on various disease processes.

Moreover, eVim has been identified in the extracellular matrix during tissue remodeling processes, including coronary artery disease, the transition of fibroblasts to the myofibroblast phenotype and bone resorption.[32,40,41] Its presence in these contexts suggests a contribution to cellular migration and tissue repair.

In some infections, pathogens or immune responses can lead to the upregulation and release of vimentin into the extracellular space.[28,40,42–45] Various forms of cellular stress, such as oxidative or endoplasmic reticulum (ER) stress, have also been associated with vimentin upregulation, potentially increasing its extracellular pool during cell activation or injuries.[46,47]

Interestingly, eVim has been implicated in autoimmune conditions, including rheumatoid arthritis, systemic lupus erythematosus and multiple sclerosis.[4,48–50] This association highlights the diverse roles of eVim in both physiological and pathological conditions. A summary of disease states and stimulators of eVim secretion is presented in Figure 1.

Vimentin, traditionally recognized as an intracellular protein forming the dynamic cytoskeletal network, has been identified on the cell surface, termed cell surface vimentin. Notably, recent observations indicate that vimentin can be incorporated onto the surfaces of fibroblasts, as well as lung and kidney epithelial cells, when externally added.[6] In addition, the fully differentiated cells, such as human type II pneumocytes that do not express vimentin, are able to anchor on their surface eVim, which shows up in the extracellular environment during inflammation.[6] This discovery unveils a novel dimension in cell pathophysiology, suggesting that cells lacking vimentin expression could potentially become targets for pathogens using this protein as a receptor or coreceptor for host cell entry. Furthermore, it implies potential involvement in processes regulated by vimentin, indicating a complex interplay with cell recognition and response through the addition of eVim. These findings propose a unique role for vimentin as both an agonist and a receptor in cell response processes, contributing to negative- and positive-feedback loops.[6,7,51]

Prior research has identified various cell surface components involved in glycocalyx formation as potential binding partners for vimentin. These components encompass CD44, the hyaluronan-mediated motility receptor (RHAMM), hyaluronic acid and *N*-acetyl glucosamine-

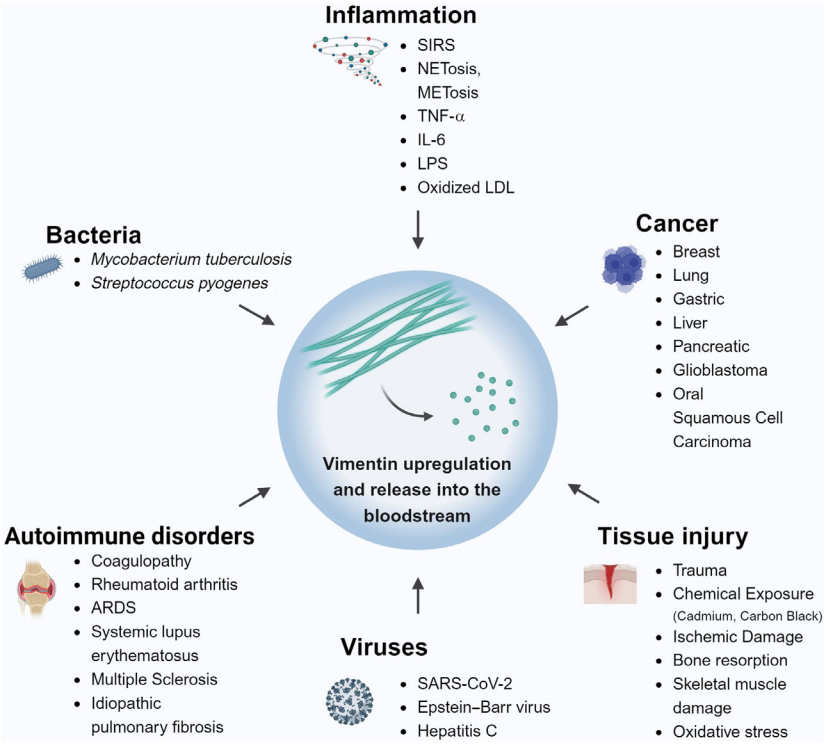

Figure 1. Conditions and stimuli that lead to the release of extracellular vimentin into the bloodstream. ARDS, acute respiratory distress syndrome; IL, interleukin; LDL, low-density lipoprotein; LPS, lipopolysaccharide; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SIRS, systemic inflammatory response syndrome; TNF-α, tumor necrosis factor-alpha.

containing (GlcNAc) structures, which have been suggested as attachment partners for vimentin on the cell surface.[52–55] In addition, β1-integrin is proposed as a vimentin-binding partner, but proteomic studies indicate that its glycosylation with N-GlcNAc is necessary for binding eVim.[54] When vimentin interacts with these surface molecules, it becomes a sufficient substrate for cell attachment and motility.[56] This intricate network of interactions expands our understanding of vimentin's multifaceted role in cellular dynamics and highlights its potential as a versatile player in cell adhesion and motility processes.

Vimentin release into the extracellular space

Vimentin observed in the extracellular space may be released from cells through various mechanisms. One mode of passive release involves vimentin being released into the extracellular space when necrosis or accidental cell rupture occurs.[32,33] In addition to the passive release, cells can actively secrete vimentin *via* the ER–Golgi apparatus as well as through unconventional type III protein secretion pathways.[57] Early studies by Gao and Sztul[58] demonstrated that Golgi elements can bind to vimentin filaments, indicating a direct interaction between these cellular components. Similarly, Mor-Vaknin *et al.*[3] found that vimentin colocalizes with the ER and Golgi apparatus. They also observed that using Golgi inhibitors, such as monensin and tunicamycin, effectively stops vimentin secretion from macrophages. Recently, a different perspective on vimentin secretion was proposed, especially in endothelial cells. This research indicates that vimentin is among the proteins externalized from endothelial cells as part of a class of nonclassically secreted proteins. These proteins lack the sequence features characteristic of those secreted through the classical ER and Golgi-mediated pathway.[57] Intriguingly, the blockade of classical secretion mechanisms, including the inhibition of ER and Golgi functions, did not impede vimentin secretion in endothelial cells. This suggests that unconventional secretion processes release proteins without utilizing the ER or Golgi apparatus in contrast to the classical ER–Golgi secretory pathway, where proteins pass through these organelles.[59] Thus, vimentin secretion appears cell-specific, potentially occurring through the ER–Golgi route and unconventional pathways. This complexity underscores the diverse mechanisms cells use to interact with their extracellular environment.

Certain cell types, particularly immune cells such as macrophages and neutrophils, may undergo ETosis (extracellular trap formation), an active form of cell death that releases cellular content in response to proinflammatory stimuli.[3,6] These extracellular traps include decondensed chromatin and other active compounds, including vimentin.[21,48]

Furthermore, vimentin may be released from cells through packaging in vimentin-containing vesicles, such as exosomes or microvesicles, freed from the cell membrane of adipocyte progenitors.[60] In addition, astrocytes become activated when the brain experiences injury or damage and respond to the wound by producing and releasing eVim in exosomes.[61–63] All those processes contribute to vimentin's controlled and targeted release into the extracellular environment that is context- and cell-dependent.

IMMUNOMODULATORY FUNCTIONS OF EXTRACELLULAR VIMENTIN

Studies demonstrating the involvement of extracellular vimentin in immune responses

The impact of the host inflammatory response is a subject of extensive research, with a particular focus on the unmodified form of eVim, which acts as a ligand for various pattern recognition receptors responsible for detecting foreign, pathogen-derived substances within host cells.[56,64,65] One such interaction involves eVim and the nucleotide-binding oligomerization domain-containing protein 2 (NOD2), which plays a critical role in the subsequent activation of nuclear factor-κB (NF-κB), a key transcription factor involved in inflammatory processes.[9] Moreover, eVim was found as a proangiogenic VEGF mimic and was proposed as a target for antiangiogenic immunotherapy.[57] Notably, the engagement of eVim with Dectin-1, an essential receptor involved in the response of macrophages to fungal infections, triggers the production of reactive oxygen species.[66,67] Moreover, eVim enhances the secretion of proinflammatory cytokines, including interleukin-6 (IL-6) and tumor necrosis factor-α, induced by oxidized low-density lipoprotein in macrophages.[10] By contrast, when lipopolysaccharide-activated dendritic cells are exposed to eVim, it alters the cytokine profile. This results in a decrease in IL-6 and IL-12 secretion while promoting the production of the anti-inflammatory molecule IL-10 and reducing type 1 T helper differentiation of naïve T cells.[11] eVim derived from adipocyte progenitors saved cells from osmotic stress, enhancing wound healing and inhibiting apoptosis.[60] Apart from its role in inflammation, eVim also plays an essential role in diapedesis, contributing to the proper distribution and expression of adhesion molecules (intercellular adhesion molecule 1 [ICAM-1], vascular cell adhesion protein 1 [VCAM-1] or integrin-β1) in lymphocytes and endothelial cells.[8] eVim's role in migration and phagocytosis in human macrophages highlights its multifaceted role in immune responses.[7] Molecular mechanisms of extracellular and cell-surface vimentin–mediated signaling pathways are presented in Figure 2.

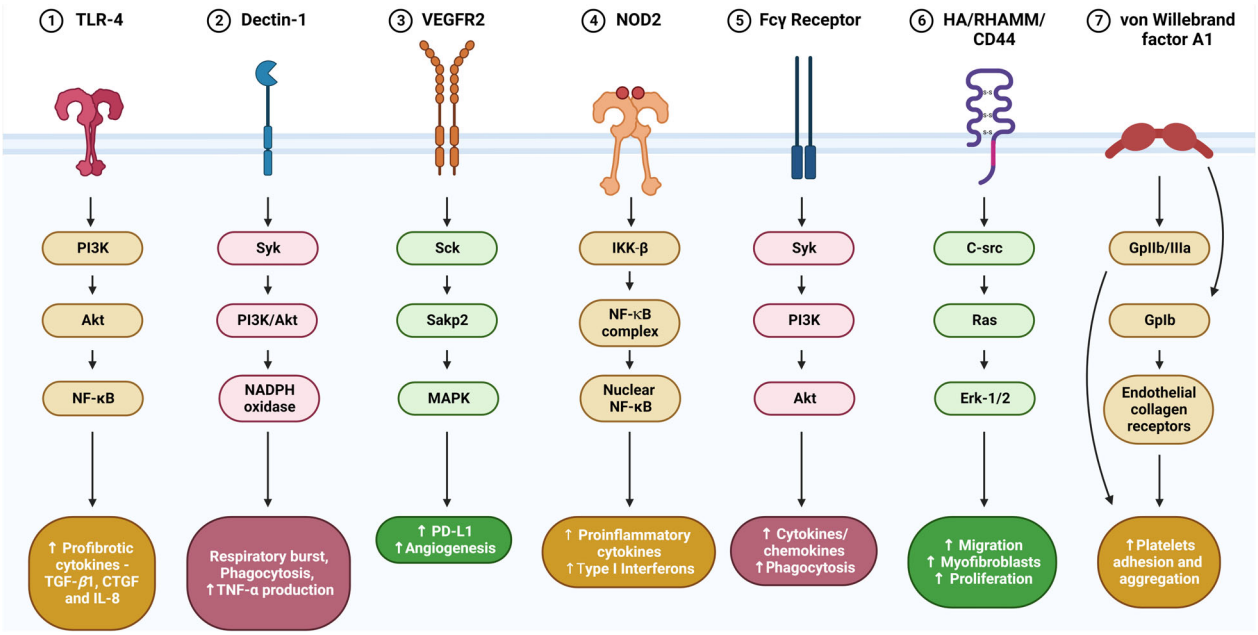

Figure 2. Molecular mechanisms of extracellular and cell-surface vimentin–mediated signaling pathways that may involve eVim receptors. **(1)** Citrullinated vimentin (CitVim) activation of nuclear factor-kappa B (NF-κB) and induction of inflammatory cytokines: CitVim activates NF-κB signaling in lung fibroblasts through a Toll-like receptor 4–dependent mechanism, leading to the production of active transforming growth factor-β1 (TGF-β1), connective tissue growth factor (CTGF) and interleukin-8 (IL-8). **(2)** eVim-mediated dectin-1 activation in human monocytes: eVim interacts with dectin-1 on human monocytes, resulting in the activation of NADPH (nicotinamide adenine dinucleotide phosphate hydrogen) oxidase, subsequent generation of reactive oxygen species and production of tumor necrosis factor-α (TNF-α), implicating eVim in the innate immune response. **(3)** eVim's role in vascular endothelial growth factor 2 (VEGFR2) signaling and tumor angiogenesis: eVim mimics VEGF and directly binds to VEGFR2, leading to increased expression of programmed death-ligand 1 (PD-L1) and enhanced tumor angiogenesis. **(4)** Vimentin's interaction with nucleotide-binding oligomerization domain-containing protein 2 (NOD2) and proinflammatory signaling: vimentin engages with NOD2, activating the NF-κB complex and its translocation into the nucleus. This results in the secretion of proinflammatory cytokines and type I interferons. **(5)** eVim-mediated phagocytosis in macrophages: eVim is implicated in triggering phagocytosis in macrophages, likely through FcγR-mediated mechanisms, highlighting its role in modulating immune cell functions. **(6)** eVim incorporation into the cell membrane and fibroblast behavior: eVim interacts with the hyaluronic acid/receptor for hyaluronan-mediated motility/CD44 complex, leading to the incorporation of eVim into the cell membrane. This interaction enhances fibroblasts' migration, proliferation and transition into myofibroblasts, contributing to tissue remodeling processes. **(7)** eVim-mediated platelet interactions: on the surface of platelets, eVim binds to the von Willebrand factor A1 domain, promoting platelet–platelet and platelet–endothelial interactions, influencing hemostasis and vascular functions. These findings collectively demonstrate the diverse roles of extracellular and cell surface vimentin in various biological processes and cellular responses, shedding light on its importance in both physiological and pathological contexts. Akt, protein kinase B; C-src, pro-oncogene tyrosine-protein kinase Src; Erk, extracellular signal-regulated kinase; HA, hyaluronic acid; IKK, IkappaB kinase complex; MAPK, mitogen-activated protein kinase; PI3K, phosphoinositide 3-kinase; Ras, rat sarcoma virus; Sakp2, S-phase kinase associated protein 2; Sck, SHC-transforming protein; Syk, spleen tyrosine kinase.

Overall, vimentin's involvement in various aspects of the host inflammatory response, including interactions with pattern recognition receptors, modulation of cytokine secretion and its impact on immune cell function, demonstrates its significance in immune regulation and the potential for therapeutic targeting in inflammatory and autoimmune diseases.

Impact of post-translational citrullination on the function of vimentin

Post-translational modifications are chemical modifications that occur on proteins after they are synthesized, and can significantly impact their structure and function.[68,69] Of the many vimentin modifications (phosphorylation, O-glycosylation and acetylation), the citrullination of vimentin has become a crucial factor influencing the immune response and inflammatory processes.[70–74]

Citrullination, involving the conversion of arginine to citrulline, is catalyzed by calcium-dependent enzymes known as peptidylarginine deiminases (PADs), particularly PAD2 and PAD4 in the case of vimentin as indicated in Figure 3a.[75–78] Human vimentin, consisting of 466 amino acids with 43 arginine residues, undergoes this modification, as illustrated in the 3D and linear amino acid representations created using AlphaFold (Figure 3b, c).[79,80]

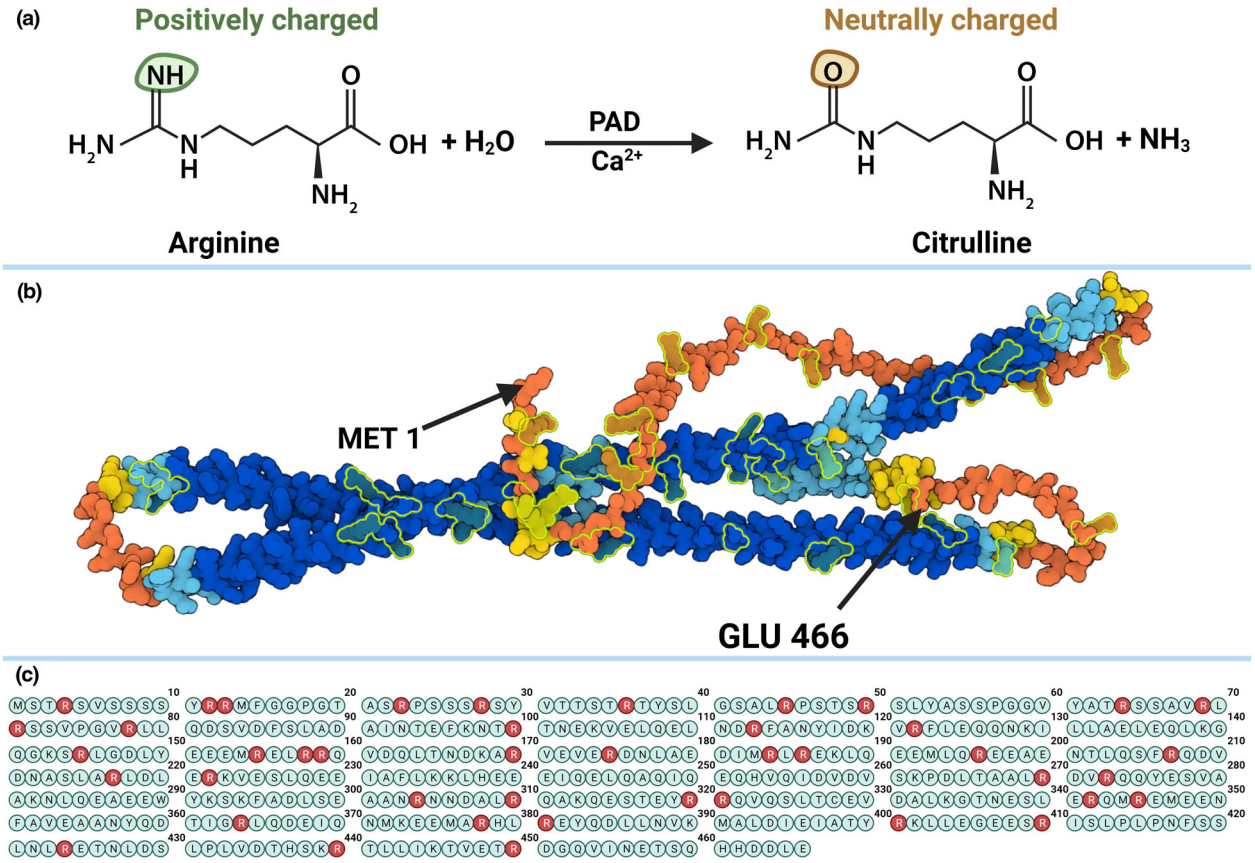

Figure 3. (a) The enzymatic conversion of arginine residues to citrulline, facilitated by peptidylarginine deiminase and calcium ions. **(b)** The 3D model of a vimentin monomer, generated using the AlphaFold and representing UniProt accession P08670, illustrates the spatial arrangement of amino acid residues. Arginine residues are depicted with a green border. **(c)** The amino acid sequence of vimentin. Arginine residues are shown in red.

A substantial quantity of arginine residues, susceptible to potential citrullination, could influence the concurrent emergence of diverse forms of citrullinated vimentin (CitVim), each exhibiting distinct properties. These variations in citrullination may have implications for the functional roles of vimentin within the extracellular environment. Despite substantial advancements in understanding the role of citrullination in certain proteins, the direct impact of CitVim on the immune response still needs to be explored. Here, we elucidate the complex role of CitVim in immune regulation and inflammatory processes. In contrast to its unmodified form, CitVim binds to HLA-DRB1, activating T cells in patients with rheumatoid arthritis and enhancing cytokine production, particularly INFγ.[81] Moreover, CitVim enhanced the proliferation capacity and secretion of proinflammatory cytokines (tumor necrosis factor-α and IL-1) in fibroblast-like synoviocytes from patients with rheumatoid arthritis and osteoarthritis. Conversely, unmodified vimentin exhibited an inhibitory effect on fibroblast-like synoviocyte proliferation, further highlighting the immunomodulatory properties of vimentin and the proinflammatory phenotype of its citrullinated form.[82] CitVim was found to activate NF-κB in a TLR4-dependent manner, producing active transforming growth factor-β1 (TGF-β1), connective tissue growth factor and IL-8 in lung fibroblasts.[4] This finding suggests that CitVim may significantly regulate inflammatory responses in various tissues and organs. CitVim directly affects osteoclasts, contributing to increased bone resorption in a mouse periodontitis model. They found suppressive effects of anti-vimentin antibodies on the receptor activator of NF-κB ligand (RANKL)–induced osteoclast genesis *in vitro*, suggesting potential therapeutic avenues for managing bone-related disorders.[40]

CitVim exhibits diverse effects on protein function, immune response and inflammatory processes. While our understanding of CitVim's role is growing, further

research is essential to elucidate its impact on the immune system entirely. Targeting CitVim and its associated pathways may hold promise for developing novel therapeutic strategies for immune-related disorders and inflammatory conditions.

ROLE OF EXTRACELLULAR VIMENTIN IN HOST–PATHOGEN INTERACTIONS

The interplay between extracellular vimentin and various pathogens

Pathogenic viruses and bacteria have evolved sophisticated strategies to infect host cells, with one common mechanism being the exploitation of cell surface vimentin to adhere to and invade host cells, facilitating infections.[83] This phenomenon has been observed in various pathogens, indicating a significant role of vimentin in host–pathogen interactions. For example, *Streptococcus agalactiae* can cause invasive meningitis in newborns by binding to vimentin on the surface of human cerebral microvascular endothelial cells, promoting bacterial colonization and invasion.[13] Similarly, *Escherichia coli* K1 relies on the interaction between cell surface vimentin and the bacterial virulence factor IbeA to invade brain endothelial cells.[84] The P1 protein, a major immunogenic protein of *Mycoplasma pneumoniae*, was found to interact with vimentin and facilitate adhesion to bronchial epithelial cells.[85] Interaction of internalin (InlF) of *Listeria monocytogenes* and surface-localized vimentin was found to be responsible for blood–brain barrier crossing and, subsequently, invasion into the brain.[86] *Mycobacterium tuberculosis*–infected monocytes had upregulated expression of cell surface vimentin on macrophages that enhanced the lysis of infected monocytes by natural killer cells.[87,88] Remarkably, vimentin has been identified as a coreceptor/attachment factor for different viruses, including human papillomavirus (HPV), Enterovirus 71, porcine reproductive and respiratory syndrome virus, cowpea mosaic virus and SARS coronaviruses, including SARS-CoV-1 and SARS-CoV-2, underscoring its potential significance in the context of viral infections.[6,12,89–91] Recently, we characterized the molecular interactions between the spike protein receptor-binding domain (S1 RBD) of SARS-CoV-2 and vimentin.[51] In this study, monolayers of recombinant human vimentin were affixed to mica surfaces and gold microbalance sensors, enabling precise measurements of its interactions with S1 RBD. In addition, the interactions of vimentin in its native extracellular form, present on the surface of fibroblast with S1 RBD, were confirmed using atomic force microscopy. Recent findings imply that externally added vimentin can stimulate phagocytosis in human macrophages, indicating a possible link between pathogen–vimentin interactions and immune responses.[7] This suggests that the exploitation of vimentin by pathogens may influence the delicate balance between infection establishment and immune defense.

POTENTIAL THERAPEUTIC IMPLICATIONS OF TARGETING EXTRACELLULAR VIMENTIN

Antimicrobial therapies

eVim serves as a critical player in pathogen survival and dissemination, making it an attractive target for novel antimicrobial strategies. Manzer *et al.*[92] identified the binding site within eVim for group B *Streptococcus* BspC, and by targeting this site with a specifically designed inhibitor, adherence and entry into the brain were successfully blocked *in vivo*. Inhibiting vimentin–pathogen interactions may impair the pathogen's ability to adhere to host tissues, invade cells or evade the immune system, thus limiting its virulence.

Vimentin acts as a coreceptor for certain coronaviruses, including SARS-CoV-1 and SARS-CoV-2. Targeting these interactions could potentially block viral entry into host cells. A clinical trial investigating vimentin-targeted therapy for coronavirus disease 2019 (COVID-19), known as humanized virus suppressing factor-variant 13 (hzVSF-v13), has shown promising results in a phase II clinical trial study. Administered to patients with moderate to severe COVID-19 pneumonia, hzVSF-v13 demonstrated a reduction in the time required to discontinue oxygen therapy and an improvement in the overall time to total recovery.[93] This monoclonal immunoglobulin G4 antibody targeting vimentin may be a potential candidate for treating severe cases of COVID-19.

We have previously revealed that antibodies targeting the C-terminal, but not the N-terminal site of vimentin, inhibited intracellular uptake of SARS-CoV-2 pseudoviruses.[6] Conversely, the N terminus of vimentin is responsible for the interaction between Enterovirus 71 and vimentin, indicating that the exploitation of cell surface vimentin is complex and may be pathogen-specific.[89] Interestingly, reducing cell surface vimentin using small interfering RNA knockdown led to a significant increase in HPV16-PsV internalization. Conversely, when vimentin was overexpressed, it had the opposite effect, decreasing HPV16-PsV internalization.[94] Carse *et al.*[18] showed that supplementation with exogenous vimentin effectively mitigates the initial stages of HPV16 pseudovirus internalization in mice.

Administration of hzVSF-v13, a humanized anti-eVim monoclonal antibody, has shown efficacy in reducing blood eVim levels in SARS-CoV-2–infected hamsters, surpassing the performance of remdesivir, a conventional

antiviral medication used for COVID-19 treatment.[28,95] Targeting eVim–pathogen interactions could be integrated into combination therapies alongside conventional antimicrobial agents. The combined therapeutic approach utilizing the vimentin-targeting antibody hzVSF and tenofovir demonstrated significant efficacy in suppressing woodchuck hepatitis virus infection in woodchucks.[96] This approach holds promise for enhancing the effectiveness of existing treatments and reducing the likelihood of pathogen resistance development.

Cancer therapies

In certain types of cancer, eVim has been linked to tumor growth, invasion and metastasis.[37,57] Inhibiting vimentin interactions with cancer cells or the tumor microenvironment may provide a new approach to impede cancer progression and improve treatment outcomes. Wu *et al.*[97] developed a vimentin-binding compound that efficiently inhibits cancer exosome release and reduces the mobility of cancer cells. In addition, vaccination with a conjugate vaccine targeting eVim has demonstrated significant tumor growth inhibition and decreased vessel density in the B16F10 melanoma tumor model.[98] Notably, in the treatment of dogs with bladder cancer, the use of the eVim-targeted vaccine CVx1 in combination with meloxicam (a nonsteroidal anti-inflammatory drug) resulted in nearly double the survival rate compared with a control group treated with carboplatin and piroxicam (another nonsteroidal anti-inflammatory drug).[99]

Immune modulation

The release of vimentin is often associated with inflammation and can significantly amplify inflammatory responses.[4,11,29] eVim plays a pivotal role in influencing immune responses by affecting the function of immune cells.[8,10,66,67,100,101]

Therapies that modulate vimentin–pathogen interactions may fine-tune immune responses and aid in controlling infections or autoimmune diseases. Thalla *et al.*[7] demonstrated that targeting surface vimentin with an anti-vimentin antibody led to a decrease in tumor necrosis factor-α–mediated macrophage activation. In the context of SARS-CoV-2 infection, the administration of hzVSF-v13 to infected hamsters resulted in reduced secretion of IL-1β and IL-8.[28] In addition, a small vimentin-binding molecule, R491, showed efficacy in suppressing intestinal inflammation. This led to a decrease in various proinflammatory cytokines, including IL-6, tumor necrosis factor-α, IL-1β, IL-17 and IL-22, by regulating regulatory T cell/type 17 T helper in acute and chronic colitis in mice.[102]

Tissue regeneration and repair

Vimentin has been implicated in tissue repair and remodeling processes.[32,40] Controlling its interactions with cells and extracellular matrix components might offer therapeutic opportunities to promote tissue regeneration in certain injuries or diseases.

Antibodies targeting vimentin have demonstrated effectiveness in inhibiting the differentiation of mesenchymal leader cells into myofibroblasts expressing α-smooth muscle actin, a key profibrotic marker.[32] Moreover, local injection of a neutralizing antibody against vimentin has proven effective in suppressing periodontal bone loss in mice.[40]

It is crucial to acknowledge that research in this area is still relatively new, and the development of therapeutic interventions based on targeting eVim interactions may require further exploration. Advancements will involve a deeper understanding of the molecular mechanisms underlying these interactions, preclinical testing and clinical trials to thoroughly assess the safety and efficacy of such therapies in humans.

DIAGNOSTIC POTENTIAL AND FUTURE PERSPECTIVES

Challenges and opportunities in translating the knowledge of extracellular vimentin into diagnostic and clinical applications

Understanding eVim's exact mechanisms of action and spectrum of functions is a complex task. Its roles and interactions in the extracellular space still need to be fully elucidated, and more research is required to decipher its functions and potential effects on various cell types and tissues. Although eVim has been proposed as a potential biomarker for multiple diseases such as glioma, coronary artery disease, sepsis and inflammatory conditions, rigorous validation studies are necessary to establish its specificity and sensitivity.[4,8,28–30,37] False-positive or false-negative results could lead to inaccurate diagnoses or treatment decisions. Developing standardized and reliable assays to detect and measure eVim is crucial for clinical use. Consistent or reliable assays could help its implementation as a diagnostic or prognostic tool.

However, overcoming the challenges while studying eVim may, as a result, create some opportunities. Detecting its presence in body fluids or tissues could aid in the early detection, diagnosis and prognosis of certain conditions. If eVim plays a role in disease progression, it could become a target for therapeutic interventions. Blocking or modulating its actions with specific antibodies could provide a novel approach to treating various

diseases, such as rheumatoid arthritis. Understanding the role of eVim in individual patients could contribute to personalized medicine approaches. Tailoring treatments based on the presence or absence of this protein and its post-translationally modified forms could lead to more effective and targeted therapies. eVim may have implications in cancer immunotherapy. It could be used as a target for immunotherapeutic strategies, such as targeted antibodies. As an extracellular protein involved in tissue repair and remodeling, eVim may have applications in regenerative medicine. Manipulating its presence or activity could enhance tissue regeneration and wound healing. Understanding the interactions of eVim with drugs or nanoparticles could lead to new drug delivery strategies, improving drug efficacy and reducing side effects.

CONCLUSION

Identifying eVim as a novel modulator of immune responses and host–pathogen interactions marks a significant advancement in immunology and infectious disease research. Traditionally recognized as an intracellular structural protein, the revelation of eVim's dual role as a damage-associated molecular pattern and its association with autoimmune diseases and cancer progression underscores its multifaceted impact on immune regulation and disease pathogenesis. Recent studies emphasize the pivotal role of eVim in activating immune cells, initiating inflammatory responses and influencing host–pathogen interactions. Its presence on the cell surface adds complexity to infection dynamics, enabling pathogens to exploit this extracellular protein for invasion, while the immune system recognizes it as a danger signal, mobilizing a defense against invading pathogens. The potential therapeutic implications of targeting eVim are promising and warrant further exploration. Manipulating its functions holds the potential for regulating immune responses, controlling autoimmune diseases and disrupting tumor progression in cancer. As our understanding of the precise mechanisms and importance of eVim continues to evolve, this emerging area of research stands poised to advance our comprehension of the intricate interactions between the immune system and infectious agents. It offers novel avenues for developing innovative therapies and interventions to combat a spectrum of diseases.

ACKNOWLEDGMENTS

This work was supported by a National Science Center under a PRELUDIUM 21 grant (UMO-2022/45/N//NZ6/01454) awarded to ŁS and by the Medical University of Białystok to PD (B.SUB.23.329).

AUTHOR CONTRIBUTIONS

Łukasz Suprewicz: Conceptualization; funding acquisition; visualization; writing – original draft; writing – review and editing. **Magdalena Zakrzewska:** Visualization; writing – review and editing. **Sławomir Okła:** Conceptualization; writing – review and editing. **Katarzyna Głuszek:** Writing – review and editing. **Alicja Sadzyńska:** Conceptualization; writing – review and editing. **Piotr Deptuła:** Funding acquisition; writing – review and editing. **Krzysztof Fiedoruk:** Conceptualization; writing – review and editing. **Robert Bucki:** Conceptualization; writing – review and editing.

CONFLICT OF INTEREST

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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