



The molecular biophysics of extracellular vimentin and its role in pathogen–host interactions

Sepideh Parvanian^{1,2,3,a}, Leila S. Coelho-Rato^{1,2,a},
John E. Eriksson^{1,2,4} and Alison E. Patteson⁵

Abstract

Vimentin, an intermediate filament protein typically located in the cytoplasm of mesenchymal cells, can also be secreted as an extracellular protein. The organization of extracellular vimentin strongly determines its functions in physiological and pathological conditions, making it a promising target for future therapeutic interventions. The extracellular form of vimentin has been found to play a role in the interaction between host cells and pathogens. In this review, we first discuss the molecular biophysics of extracellular vimentin, including its structure, secretion, and adhesion properties. We then provide a general overview of the role of extracellular vimentin in mediating pathogen–host interactions, with a focus on its interactions with viruses and bacteria. We also discuss the implications of these findings for the development of new therapeutic strategies for combating infectious diseases.

Addresses

¹ Turku Bioscience Centre, University of Turku and Åbo Akademi University, 20520, Turku, Finland

² Faculty of Science and Engineering, Cell Biology, Åbo Akademi University, 20520, Turku, Finland

³ Center for Systems Biology, Massachusetts General Hospital Research Institute and Harvard Medical School, Boston, MA 02114, USA

⁴ Euro-Bioimaging ERIC, 20520, Turku, Finland

⁵ Physics Department and BiolInspired Institute, Syracuse University, Syracuse, NY, 13244, USA

Corresponding author: Patteson, Alison E. (aepattes@syr.edu)

^a Denotes co-first author.

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Introduction

Vimentin is an intermediate filament protein that is primarily expressed by the cells of mesenchymal origin such as fibroblasts, endothelial and hematopoietic cells. However, in certain pathological conditions such as

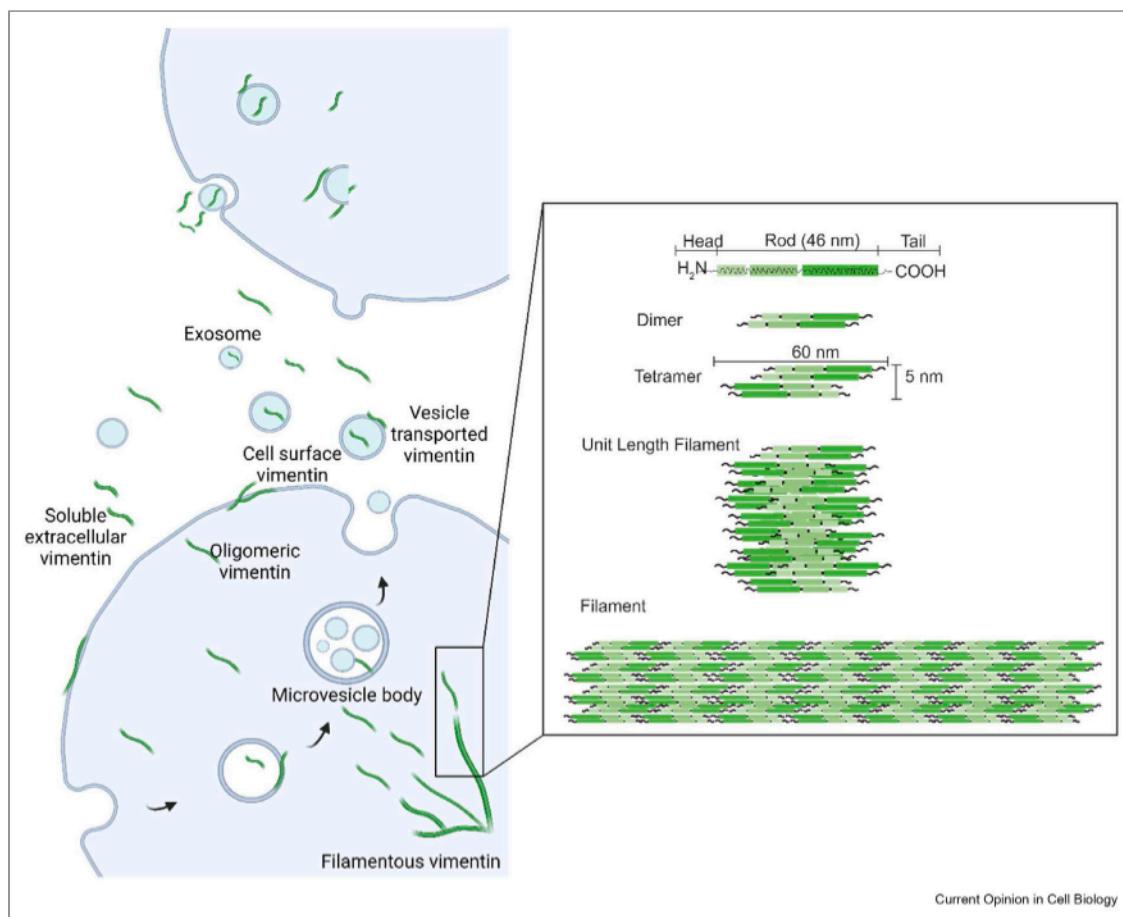
infection and injury, epithelial cells can also express vimentin [1–3]. For instance, epithelial cells such as columnar and basal cells in the lungs, when damaged or infected, express high levels of vimentin [4,5]. Modulation of vimentin expression impacts pathogen invasion and pathogen infection that changes the normal function and organization of intracellular vimentin. During infection, viruses manipulate the host's vimentin filaments to facilitate infection [6,7]. In addition to intracellular vimentin, extracellular vimentin including cell surface and circulating vimentin has been reported to function as a receptor and co-receptor for pathogens including viruses and bacteria either to facilitate or to restrict the cellular invasion [8–10]. Furthermore, extracellular vimentin secreted by different cells such as activated macrophages might be a component of the host defense system that participates in pathogen trapping and elimination [9–11]. Interestingly, anti-vimentin antibodies or soluble vimentin have been reported to inhibit the binding of bacterial microaggregates or viral particles [2,12–14].

Molecular biophysics of extracellular vimentin

Structure

New studies have revealed that extracellular vimentin appears in predominantly short non-filamentous forms in contrast to the filamentous cytoskeletal vimentin networks that are prominently displayed in mesenchymal cells. Vimentin is a 54kD type III intermediate filament comprised of 466 amino acids (UniProtKB-P08670). The assembly of vimentin molecules into larger structures is a complex multi-scale process. A single vimentin polypeptide forms a central alpha-helical coil flanked by a head (N) and tail (C) chains [15]. In the cell, vimentin polypeptide coils are woven together to create elongated dimers of two parallel polypeptide chains. Next, vimentin dimers combine in an anti-parallel and staggered manner to form a vimentin tetramer. The basic building block of vimentin filament assembly is termed a unit length filament (ULF), comprised of approximately 8 tetramers and 60 nm in length (Figure 1) [16]. ULFs undergo longitudinal end-to-end annealing with one another and with other growing filaments to form expansive cytoskeletal networks. In contrast, immunofluorescence images of

Figure 1



Structure and secretion of extracellular vimentin. Vimentin is a 54 kDa rod-shaped protein. Single vimentin monomers combine in parallel to form dimers (shown staggered for visualization), which assemble into tetramers, and eight tetramers form a 60-nm long rod-like structure called a unit-length filament. The unit-length filament forms the repeating units of a vimentin fiber. Extracellular vimentin is much smaller than the full filaments in the cells and is typically only 228–684 kD, corresponding to 1–3 tetrameres in size. Secretion of soluble vimentin in human endothelial cells occurs via unconventional protein secretion (UPS), in particular type III UPS. Unlike classical secretion, type III UPS involves recruitment of cargo proteins into vesicular compartments, such as endosomes and autophagosome organelles, that fuse with the plasma membrane to release proteins into the extracellular space. Extracellular vimentin also appears as a signaling agent on exosomes ("exosomal vimentin"), which are released via the type III UPS pathway and which can be taken up into other receptor cells.

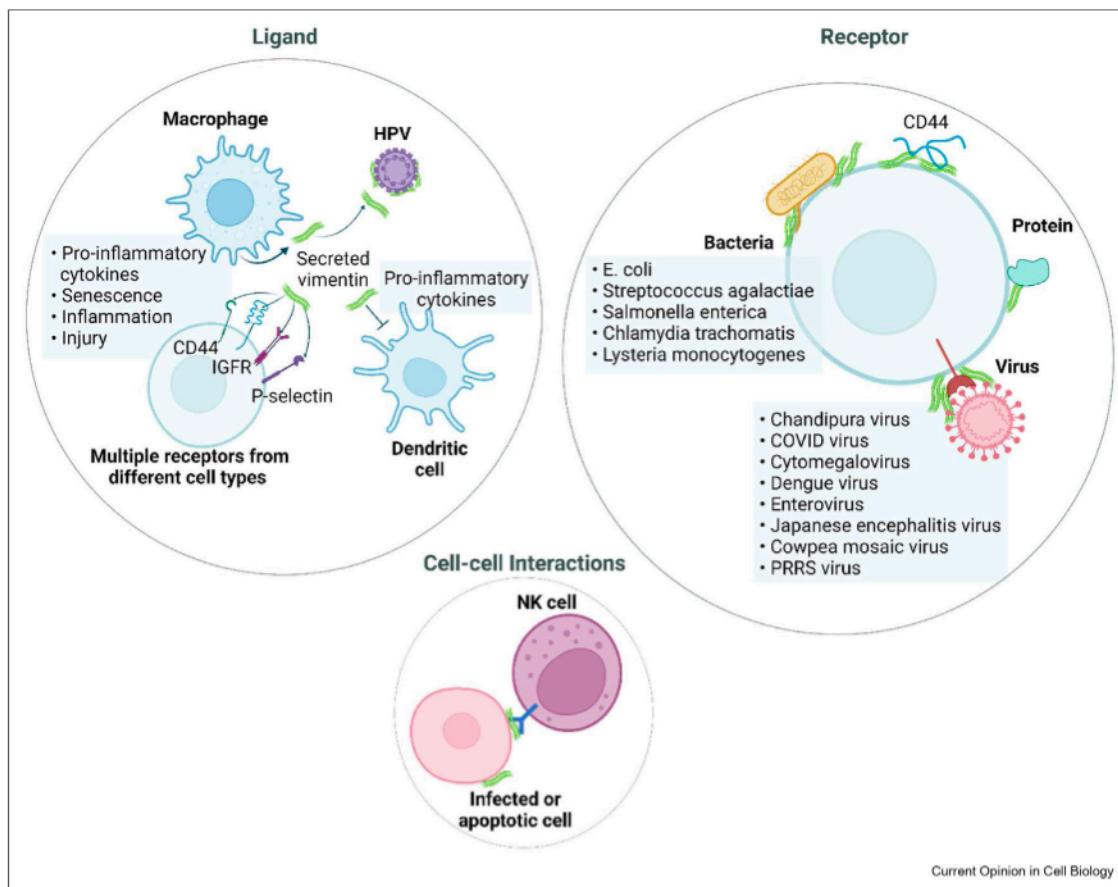
extracellular vimentin do not show long connected filaments typical of the cytoskeleton but instead appear as short segments or small agglomerates [8,13,17]. A recent study by Hoang and Ise characterized the molecular structure of extracellular vimentin in human glioma KNS-42 cells. Combining surface protein biotinylation and gel electrophoresis techniques, the authors found the structure of extracellular vimentin to be mostly in the form of oligomers, 4–12-mers of approximately 228–684 kD [18]. These sizes correspond to approximately 1–3 tetrameres, which is smaller than a ULF (8 tetrameres). Interestingly, the authors also detected other intermediate filaments of similar size on the extracellular surface of cells, including GFAP in KNS-42 cells, desmin in C2C12 mouse myoblasts, and peripherin in rat pheochromocytoma PC-12 cells [18].

Taken together, these studies suggest vimentin and other intermediate filament proteins appear in unusually small structures on the cell surface (see Figure 1).

Secretion

The presence of extracellular vimentin is associated with inflammatory conditions (Figure 2). For example, extracellular vimentin [19] can be stimulated *in vitro* by exposing cells to inflammatory-related signals, such as angiogenic growth factors [20] or the spike protein from the SARS virus [21]. In addition, activated macrophages secrete vimentin, and neutrophils release vimentin during NETosis, a process in which neutrophils expel DNA webs to entrap bacteria [11,13]. Conventionally, secreted proteins carry a signaling peptide that directs their insertion into the endoplasmic reticulum where

Figure 2



Roles of the extracellular vimentin pool in the immune system. Extracellular vimentin can act as a ligand or as a receptor/co-receptor for different cell types. Vimentin is released by activated macrophages and participates in pathogen trapping. In response to injury and inflammatory signals, it can also directly bind and activate cell-surface receptors such as CD44, IGFR, and P-selectin. Due to its affinity to the lipid bilayer and polysaccharides, extracellular vimentin can be found at the cell surface, where it may bind proteins and different pathogens, including various viruses and bacteria, and facilitate infection. Moreover, natural killer (NK) cells can target infected cells by recognizing extracellular vimentin on the cell surface.

they exit via vesicles to reach the Golgi apparatus and then the plasma membrane to be released into extracellular space [22,23]. Early reports of extracellular vimentin released by macrophages showed colocalization of vimentin with the Golgi and the application of Golgi blockers eliminated the release of vimentin, suggesting vimentin was secreted through the Golgi apparatus [11]. However, unlike traditionally secreted proteins, intermediate filaments lack signal peptides for recruitment to the cell membrane [18]. Thus, there is still open questions about how vimentin is released into the extracellular space.

In a recent search for possible regulated pathways for vimentin secretion, a study by Beijnum et al. has revealed some new clues about possible secretion routes [20]. In this study, the authors screened for possible vimentin secretion pathways by testing the effects of 28 known regulators of various cellular secretion mechanisms on the

presence of extracellular vimentin in human endothelial cells. Interestingly, inhibitors of classical secretion did not block vimentin secretion, but vimentin secretion was blocked by inhibitors of unconventional protein secretion (UPS) pathways, in particular type III UPS (Figure 1) (Unconventional Protein Secretion Pathways Box). The type III UPS pathway involves cargo uptake into endocytic compartments that then fuse with the plasma membrane and allow release into the extracellular space [22,23]. This pathway allows for the transport of proteins without a signal peptide or transmembrane domain for translocation across the plasma membrane. These results suggest the involvement of secretory organelles by UPS pathways to release vimentin. UPS is triggered by cellular stress and inflammation, consistent with the inflammatory contexts extracellular vimentin is found. Interestingly, vimentin has also been reported in extracellular vesicles [24,25], which are also released through type III UPS pathways.

Unconventional Protein Secretion Pathways

In recent years, research has shown that besides the conventional endoplasmic reticulum–Golgi secretory pathway, there are additional ways through which proteins can be exported. These alternative routes are termed unconventional protein secretion (UPS) pathways, and they are capable of secreting proteins lacking a signal sequence (leaderless proteins). There are currently four types of UPS. The release of extracellular vimentin by tumor endothelial cells has been associated with type III UPS. Type III UPS proceeds via endosomes and autophagosomes organelles that become secretory and fuse with the plasma membrane to release leaderless cargo proteins. With few exceptions, UPS is largely triggered by cellular stress.

Adhesion to the cell surface

The mechanisms of adhesion of extracellular vimentin to the cell surface are not yet fully understood, but new studies are pointing to at least three main ways in which vimentin may adhere to the cell surface. First, specific binding protein receptors for vimentin have been identified, such as in insulin-like growth factor 1 receptor (IGF1R) [26]. Second, vimentin and other intermediate filaments have an affinity for phospholipids, such that vimentin may interact directly with the cell's outer lipid bilayer [18]. Third, vimentin has an affinity for polysaccharides, specifically a selective interaction with N-acetylglucosamine which is a rich component of hyaluronic acid and heparin, which comprise parts of the cell's glycocalyx [27,28]. It is not yet clear to what extent each of these interactions plays in vimentin's binding and adhering to pathogens on the cell surface. It is tempting to speculate that vimentin in the cell's thick outer glycocalyx layer would serve as a useful binding site for pathogens, trapping pathogens near the cell surface where it could ultimately be delivered to specific cell surface receptors and uptake into the host cell. Interestingly, a recent study also found enrichment of extracellular vimentin at the site of primary cilia in A549 cells, where vimentin co-localized with SARS-CoV-2 spike proteins [8]; yet, it is not yet clear how vimentin is recruited to and adheres at the sites of primary cilia.

The molecular biophysics of extracellular vimentin is crucial in determining its functions in physiological and pathological conditions. In the next section, we will discuss the role of extracellular vimentin in pathogen–host interactions as an example to demonstrate that its

role extends beyond being secreted from cells. This will highlight the significance of extracellular vimentin as a potential therapeutic target in infectious diseases.

Extracellular vimentin in host–pathogen interactions

Bacterial infection

Numerous studies have reported vimentin-dependent mechanisms involved in host cell invasion of bacteria, such as *E. coli* associated with bacterial meningitis. In human meningitis, *E. coli* K1 binds to vimentin on the surface of brain microvascular endothelial cells through its virulence factor IbeA. Through this interaction, vimentin mediates signaling pathways that are required for *E. coli* K1 invasion. In this respect, vimentin plays an important role in gastrointestinal *E. coli* recognition and subsequent innate immune signaling activation [29,30]. Furthermore, surface vimentin has been reported to act as a surface receptor to mediate matrix stiffness on the invasion of human microvascular endothelial cells (HMEC-1) by *Listeria monocytogenes* [31,32]. During the pathogenesis of meningitis, surface vimentin interacts with a surface antigen I/II protein BspC of *Streptococcus agalactiae* to promote bacterial adherence to the endothelium of the brain and accelerate inflammation [33]. In addition, host cell surface vimentin is involved in recognizing gastrointestinal *E. coli* and mediating innate immune signaling. It does so by acting as a receptor for adherent-invasive *E. coli* strains (AIEC) or as an intracellular pattern recognition receptor to recognize bacterial peptidoglycan fragments [34–36]. Cell surface vimentin is also found on the surface of monocytes infected with *Mycobacterium tuberculosis*. It serves as a ligand for the NKp46 receptor, used by natural killer cells to target the infected monocytes. Treatment with an antibody against vimentin had a negative impact on the lysis of monocytes by natural killer cells [37]. Moreover, bacteria such as *Salmonella enterica* (serovar Typhimurium) and *Chlamydia trachomatis* recruit and remodel intracellular or cell surface vimentin to facilitate infection by mediating pathogen binding and intracellular innate immune signaling [3,10,38,39].

Viral infection

Vimentin also participates in viral invasion by different types of viruses with DNA, single-stranded RNA, and double-stranded RNA genomes [9]. Extracellular vimentin can mediate viral infection by acting as a receptor, co-receptor, or restriction factor [8,9,40]. Extracellular vimentin is proposed to act as a receptor or co-receptor for the invasion of severe acute respiratory syndrome coronavirus (SARS-CoV) and SARS-CoV-2. The interaction between extracellular vimentin and SARS-CoV spike protein is thought to support the docking of the virus at the cell surface and facilitate the entrance of the virus into the host cell. Vimentin-ACE2 (angiotensin-converting enzyme 2) interaction acts as a

SARS-CoV-2 docking platform at the cell surface [8], and the interaction between vimentin and SARS-CoV-2 is made via the SARS-CoV-2 spike-protein receptor binding domain [14,42]. Antibodies against extracellular vimentin supported the role of vimentin in mediating SARS-CoV-2 cell entry by blocking host cell invasion of SARS-CoV-2 pseudoviruses *in vitro* [13].

Extracellular vimentin also facilitates the attachment, entry, and internalization of different types of viruses into the host cells such as the Chandipura virus [45], Japanese encephalitis virus [46], porcine reproductive and respiratory syndrome virus [47], and cowpea mosaic virus [41]. Surface vimentin is involved in the infection of vascular endothelial cells by facilitating the adsorption of dengue virus (DENV). The direct interaction of the rod domain of superficial vimentin on vascular endothelial cells with the viral protein DENV-2 envelope protein domain III mediates the infection [43]. Enterovirus 71 interacts with the N-terminus of the host cell surface vimentin as an attachment site to proceed with the infection [12], and interestingly, enterovirus proteins can increase the expression of the virus receptor vimentin [44].

On the other hand, vimentin can act not only as a receptor but rather as a restriction factor in mediating the internalization and infection of human papillomavirus (HPV). Both soluble and surface extracellular vimentin have been shown to limit the internalization of the virus into epithelial cells by either direct contact or steric hindrance. Downregulation of surface vimentin significantly increases the infectious internalization of HPV, while overexpression of vimentin led to a substantial increase in viral uptake [48]. Extracellular vimentin in both cell surface and soluble exogenous forms has been shown to modulate the infectious potential of HPV pseudovirus (HPV16-PsVs) by inhibiting virus internalization [48,49].

While this review here focuses on extracellular vimentin, it is worth noting that once a virus invades a host, the presence of intracellular vimentin also plays a role in viral transport. For instance, recent studies have shown that intracellular vimentin reorganizes upon infection and serves as a protective scaffold for Zika virus replication [50], reorganizes and regulates nonstructural protein expression with human enterovirus [51], increases the release of influenza A virus by supporting endosome maturation [52], and inhibits fusion and maturation of human parainfluenza virus type 3 inclusion bodies [53]. Further, new data are showing vimentin-targeting small molecule compounds can reduce virus-related endocytosis, endosomal trafficking, and exosomal release as well as reduce bleomycin-induced lung injury and fibrosis in SARS-CoV-2 rat models [54].

Open questions

Many questions remain to be answered, including what are the benefits of extracellular vimentin? Extracellular vimentin is often found in the context of inflammation and disease and can be hijacked by viruses and bacteria to invade host cells. It is not yet clear what benefits are gained by the presence of vimentin in the extracellular space. One intriguing idea is that the main function of extracellular vimentin may be in serving as a signaling agent to other receptor cells. Some of the most compelling evidence for this is the work on exosomal vimentin, defined here as vimentin released via exosomes into the extracellular space [25,55]. The release of exosomal vimentin has been reported for astrocytes and adipocyte progenitor cells and the presence of vimentin on exosomes has been shown to be critical to elicit and promote wound healing responses, presumably via promoting the signal carrier function of exosomes to modify the functions of other cell types.

There is strong evidence that vimentin filaments are actively disassembled prior to being released into the extracellular space. Vimentin disassembly involves different post-translational modifications often via phosphorylation. Certain modified forms of extracellular vimentin, such as citrullinated vimentin, is being recognized for its role in pathological conditions, such as fibrosis and rheumatoid arthritis. Identifying specific vimentin modifications in the extracellular environment will help us recognize the regulated pathways that release extracellular vimentin under different conditions and may help elucidate specific domains of vimentin to target against different pathogens.

One major challenge to understanding the functional roles of extracellular vimentin is vimentin's biochemical and functional diversity. Cytoskeletal vimentin is known for playing dual overarching roles as a physical scaffold that provides mechanical strength and also a integrator of diverse biochemical signals, recruiting and localizing proteins to mediate signal transduction. Thus, vimentin is a great multitasker, positioned as a crucial player in cell migration, cell adhesion, and intracellular transport. Vimentin is only found in multicellular organisms, marking the onset of multicellularity during evolution and its associated structural and biochemical challenges. Vimentin's presence in various cell types and tissues likely evolved to fulfil these diverse structural requirements. The vimentin molecule has a complex structure with many binding sites, allowing it to be involved with many different types of multiprotein complexes and utilized under various cellular contexts. Notably, even slight modifications to vimentin's amino acids can yield opposite downstream effects due to altered binding with other proteins [56]. The structural and chemical diversity of vimentin adds an additional layer of complexity to the

problem of understanding extracellular vimentin, as its presence and its functional role could be regulated by many different cellular pathways in cell-specific and tissue-specific manners.

One last question is whether there are any active clearance mechanisms of extracellular vimentin. Cytoskeletal actin, for example, when released into the extracellular environment is promptly scavenged by plasma proteins [57]. Are there analogous methods of clearing up extracellular vimentin, and if so, can we exploit them as a preventative measure against different pathogens? One thing is clear. More detailed work is needed to understand the fundamental roles of extracellular vimentin and its impacts on translational research and into the clinic.

Concluding remarks

The extracellular form of vimentin has emerged as an important mediator of host–pathogen interactions. Its ability to interact with both viruses and bacteria highlights its potential as a therapeutic target for the prevention and treatment of infectious diseases. Investigating the clinical potential of vimentin as a binding molecule to recognize and facilitate the entry of pathogens, or as an inhibitory molecule to block pathogen internalization, could be a promising avenue for future research. However, further studies are needed to understand the involvement of vimentin in the pathogenesis of viral infections, including its cellular localization, conformational arrangements, and function-related post-translational modifications. Overall, a better understanding of the role of extracellular vimentin in host–pathogen interactions could lead to the development of new and effective strategies to combat infectious diseases.

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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

Data will be made available on request.

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References

Papers of particular interest, published within the period of review, have been highlighted as:

- * of special interest
- 1. Rogel MR, Soni PN, Troken JR, Sitkov A, Trejo HE, Ridge KM: **Vimentin is sufficient and required for wound repair and remodeling in alveolar epithelial cells.** *Faseb J* Nov. 2011, **25**: 3873–3883, <https://doi.org/10.1096/fj.10-170795>.
- 2. Babrak L, Danelishvili L, Rose SJ, Kornberg T, Bermudez LE: **The environment of *Mycobacterium avium* subsp. *hominis* microaggregates induces synthesis of small proteins associated with efficient infection of respiratory epithelial cells.** *Infect Immun* Feb. 2015, **83**:625–636, <https://doi.org/10.1128/IAI.02699-14>.
- 3. Mak TN, et al.: **Propionibacterium acnes host cell tropism contributes to vimentin-mediated invasion and induction of inflammation.** *Cell Microbiol* 2012, **14**:1720–1733, <https://doi.org/10.1111/j.1462-5822.2012.01833.x>.
- 4. Broers JLV, et al.: **Expression of intermediate filament proteins in fetal and adult human lung tissues.** *Differentiation* May 1989, **40**:119–128, <https://doi.org/10.1111/j.1432-0436.1989.tb00821.x>.
- 5. Yang Y, et al.: **Spatial-temporal lineage restrictions of embryonic p63+ progenitors establish distinct stem cell pools in adult airways.** *Dev Cell* Mar. 2018, **44**:752, <https://doi.org/10.1016/j.devcel.2018.03.001>.
- 6. He C, et al.: **Host cell vimentin restrains *Toxoplasma gondii* invasion and phosphorylation of vimentin is partially regulated by interaction with TgROP18.** *Int J Biol Sci* 2017, **13**: 1126–1137, <https://doi.org/10.7150/ijbs.21247>.
- 7. Novoa RR, Calderita G, Arranz R, Fontana J, Granzow H, Risco C: **Virus factories: associations of cell organelles for viral replication and morphogenesis.** *Biol Cell* Feb. 2005, **97**:147–172, <https://doi.org/10.1042/BC20040058>.
- 8. Lalioti V, et al.: **Cell surface detection of vimentin, ACE2 and SARS-CoV-2 Spike proteins reveals selective colocalization at primary cilia.** *Sci Rep* Apr. 2022, **12**, 1, <https://doi.org/10.1038/s41598-022-11248-y>.
- 9. Ramos I, Stamatakis K, Oeste CL, Pérez-Sala D: **Vimentin as a multifaceted player and potential therapeutic target in viral infections.** *Int J Mol Sci* Jun. 2020, **21**, <https://doi.org/10.3390/ijms21134675>.
- 10. Mak TN, Brüggemann H: **Vimentin in bacterial infections.** *Cells* Apr. 2016, **5**:18, <https://doi.org/10.3390/cells5020018>.
- 11. Mor-Vaknin N, Punturieri A, Sitwala K, Markovitz DM: **Vimentin is secreted by activated macrophages.** *Nat Cell Biol* Jan. 2003, **5**, 1, <https://doi.org/10.1038/ncb898>.
- 12. Du N, et al.: **Cell surface vimentin is an attachment receptor for enterovirus 71.** *J Virol* May 2014, **88**:5816–5833, <https://doi.org/10.1128/JVI.03826-13>.
- 13. Suprawicz Ł, et al.: **Extracellular vimentin as a target against SARS-CoV-2 host cell invasion.** *Small* 2022, **18**: 2105640, <https://doi.org/10.1002/smll.202105640>.

This research showed extracellular vimentin interacts with the SARS-CoV-2 spike protein and that antibodies targeting vimentin can block *in vitro* uptake of SARS-CoV-2 pseudo-viruses.

14. Amraei R, et al.: **Extracellular vimentin is an attachment factor that facilitates SARS-CoV-2 entry into human endothelial cells.** In *Proceedings of the national Academy of Sciences of the United States of America*; 2022, <https://doi.org/10.1073/pnas.2113874119>.

15. Sapra KT, Medalia O: **Bend, push, stretch: remarkable structure and mechanics of single intermediate filaments and meshworks.** *Cells* Aug. 2021, 10:1960, <https://doi.org/10.3390/cells10081960>.

16. Vermeire P-J, et al.: **Molecular interactions driving intermediate filament assembly.** *Cells* Sep. 2021, 10:2457, <https://doi.org/10.3390/cells10092457>.

17. Thalla DG, Rajwar AC, Laurent AM, Becher JE, Kainka L, Lautenschläger F: **Extracellular vimentin is expressed at the rear of activated macrophage-like cells: potential role in enhancement of migration and phagocytosis.** *Front Cell Dev Biol* 2022, 10, <https://doi.org/10.3389/fcell.2022.891281>.

This work explores extracellular vimentin in activated macrophages. Using patterned lines, it was shown extracellular vimentin is not distributed equally along the surface of the cells and is primarily in the "back" of the cell. Extracellular vimentin further enhances migration and phagocytosis of macrophage-like cells.

18. Hwang B, Ise H: **Multimeric conformation of type III intermediate filaments but not the filamentous conformation exhibits high affinity to lipid bilayers.** *Gene Cell* Jun. 2020, 25:413–426, <https://doi.org/10.1111/gtc.12768>.

19. Sun S, et al.: **Proteomics of hepatocellular carcinoma: serum vimentin as a surrogate marker for small tumors (≤ 2 cm).** *J Proteome Res* Apr. 2010, 9:1923–1930, <https://doi.org/10.1021/pr901085z>.

20. van Beijnum JR, et al.: **Extracellular vimentin mimics VEGF and is a target for anti-angiogenic immunotherapy.** *Nat Commun* May 2022, 13, 1, <https://doi.org/10.1038/s41467-022-30063-7>.

21. Yu YT-C, et al.: **Surface vimentin is critical for the cell entry of SARS-CoV.** *J Biomed Sci* Jan. 2016, 23:14, <https://doi.org/10.1186/s12929-016-0234-7>.

This research shows a direct interaction between cell surface vimentin and the SARS-CoV spike protein. Cell surface vimentin was found to be increased in Vero E6 cells upon exposure to SARS-CoV virus-like particles, and treatment of cells with anti-vimentin antibodies was shown to reduce uptake of the SARS-CoV virus-like particles.

22. Rabouille C: **Pathways of unconventional protein secretion.** *Trends Cell Biol* Mar. 2017, 27:230–240, <https://doi.org/10.1016/j.tcb.2016.11.007>.

23. Filaquier A, Marin P, Parmentier M-L, Villeneuve J: **Roads and hubs of unconventional protein secretion.** *Curr Opin Cell Biol* Apr. 2022, 75:10272, <https://doi.org/10.1016/j.ceb.2022.02.006>.

24. Parvanian S, et al.: **Exosomal vimentin from adipocyte progenitors accelerates wound healing.** *Cytoskeleton* 2020, 77: 399–413, <https://doi.org/10.1002/cm.21634>.

25. Parvanian S, et al.: **Exosomal vimentin from adipocyte progenitors Protects fibroblasts against osmotic stress and inhibits Apoptosis to enhance wound healing.** *IJMS* Apr. 2021, 22:4678, <https://doi.org/10.3390/ijms22094678>.

This study shows exosomal vimentin enhances in vivo wound healing by protecting fibroblasts against osmotic stress and suggests exosomal vimentin is important for conveying stress signals to other cell types to restore balance.

26. Shigyo M, Kuboyama T, Sawai Y, Tada-Umezaki M, Tohda C: **Extracellular vimentin interacts with insulin-like growth factor 1 receptor to promote axonal growth.** *Sci Rep* Dec. 2015, 5: 12055, <https://doi.org/10.1038/srep12055>.

27. Komura K, Ise H, Akaike T: **Dynamic behaviors of vimentin induced by interaction with GlcNAc molecules.** *Glycobiology* Dec. 2012, 22:1741–1759, <https://doi.org/10.1093/glycob/cws118>.

28. Bucki R, et al.: **Extracellular vimentin is sufficient to promote cell attachment, spreading, and motility by a mechanism involving N-acetyl glucosamine-containing structures.** *J Biol Chem* Jun. 2023:104963, <https://doi.org/10.1016/j.jbc.2023.104963>.

29. Chi F, et al.: **Vimentin-mediated signalling is required for IbeA+ *E. coli* K1 invasion of human brain microvascular endothelial cells.** *Biochem J* Mar. 2010, 427:79–90, <https://doi.org/10.1042/BJ20091097>.

30. Chi F, Bo T, Wu C-H, Jong A, Huang S-H: **Vimentin and PSF act in concert to regulate IbeA+ *E. coli* K1 induced activation and nuclear translocation of NF- κ B in human brain endothelial cells.** *PLoS One* Apr. 2012, 7, e35862, <https://doi.org/10.1371/journal.pone.0035862>.

31. Bastounis EE, Yeh Y-T, Theriot JA: **Matrix stiffness modulates infection of endothelial cells by *Listeria monocytogenes* via expression of cell surface vimentin.** *MBio* Jul. 2018, 29: 1571–1589, <https://doi.org/10.1093/mboz/E18-04-0228>.

This interesting paper shows that *in vitro* host cell infection by the bacterium *Listeria monocytogenes* increases with the stiffness of the cell's microenvironment. Isolating cell surface proteins and immunofluorescence imaging showed that cell surface vimentin was serving as an attachment receptor for facilitating bacterial entry and its expression levels increased with substrate stiffness.

32. Ghosh P, et al.: **Invasion of the brain by *Listeria monocytogenes* is mediated by InlF and host cell vimentin.** *mBio* Feb. 2018, 9, e00160, <https://doi.org/10.1128/mBio.00160-18>.

33. Deng L, et al.: **The Group B Streptococcal surface antigen I/II protein, BspC, interacts with host vimentin to promote adherence to brain endothelium and inflammation during the pathogenesis of meningitis.** *PLoS Pathog* Jun. 2019, 15, e1007848, <https://doi.org/10.1371/journal.ppat.1007848>.

34. Stevens C, et al.: **The intermediate filament protein, vimentin, is a regulator of NOD2 activity.** *Gut* May 2013, 62:695–707, <https://doi.org/10.1136/gutnl-2011-301775>.

35. Henderson P, Wilson DC, Satsangi J, Stevens C: **A role for vimentin in Crohn disease.** *Autophagy* Nov. 2012, 8: 1695–1696, <https://doi.org/10.4161/auto.21690>.

36. Mor-Vaknin N, et al.: **Murine colitis is mediated by vimentin.** *Sci Rep* Dec. 2013, 3:1045, <https://doi.org/10.1038/srep01045>.

37. Garg A, et al.: **Vimentin expressed on Mycobacterium tuberculosis-infected human monocytes is involved in binding to the NKp46 receptor.** *J Immunol* Nov. 2006, 177: 6192–6198, <https://doi.org/10.4049/jimmunol.177.9.6192>.

38. Kumar Y, Valdivia RH: **Actin and intermediate filaments stabilize the Chlamydia trachomatis vacuole by forming dynamic structural scaffolds.** *Cell Host Microbe* Aug. 2008, 4: 159–169, <https://doi.org/10.1016/j.chom.2008.05.018>.

39. Guignot J, Servin Alain L: **Maintenance of the *Salmonella*-containing vacuole in the juxtanuclear area: a role for intermediate filaments.** *Microb Pathog* Nov. 2008, 45:415–422, <https://doi.org/10.1016/j.micpath.2008.09.007>.

40. Li Z, Paulin D, Lacolley P, Coletti D, Agbulut O: **Vimentin as a target for the treatment of COVID-19.** *BMJ Open Resp Res* Sep. 2020, 7, e000623, <https://doi.org/10.1136/bmjjresp-2000623>.

41. Koudelka KJ, Destito G, Plummer EM, Trauger SA, Siuzdak G, Manchester M: **Endothelial targeting of cowpea mosaic virus (CPMV) via surface vimentin.** *PLoS Pathog* May 2009, 5, e1000417, <https://doi.org/10.1371/journal.ppat.1000417>.

42. Deptula P, et al.: **Physicochemical nature of SARS-CoV-2 spike protein binding to human vimentin.** *ACS Appl Mater Interfaces* Jul. 2023, 15:34172–34180, <https://doi.org/10.1021/acsami.3c03347>.

43. Yang J, et al.: **Superficial vimentin mediates DENV-2 infection of vascular endothelial cells.** *Sci Rep* Dec. 2016, 6:38372, <https://doi.org/10.1038/srep38372>.

44. Wang W, et al.: **Enterovirus A71 capsid protein VP1 increases blood–brain barrier permeability and virus receptor vimentin on the brain endothelial cells.** *J Neurovirol* 2020, 26:84–94, <https://doi.org/10.1007/s13365-019-00800-8>.

45. Kavathekar VK, Dhanavade MJ, Sonawane KD, Sonawane KD, Balakrishnan A, Balakrishnan Anukumar: **Role of cell surface vimentin in Chandipura virus replication in Neuro-2a cells.** *Virus Res* Aug. 2020, 285, <https://doi.org/10.1016/j.virusres.2020.198014>.

46. Liang J-J, Yu C-Y, Liao C-L, Lin Y-L: **Vimentin binding is critical for infection by the virulent strain of Japanese encephalitis virus.** *Cell Microbiol* Sep. 2011, **13**:1358–1370, <https://doi.org/10.1111/j.1462-5822.2011.01624.x>.

47. Kim J-K, Fahad A-M, Shanmukhappa K, Kapil S: **Defining the cellular target(s) of porcine reproductive and respiratory syndrome virus blocking monoclonal antibody 7G10.** *J Virol* Jan. 2006, **80**:689–696, <https://doi.org/10.1128/JVI.80.2.689-696.2006>.

48. Schäfer G, Graham LM, Lang DM, Blumenthal MJ, Bergant Marušić M, Katz AA: **Vimentin modulates infectious internalization of human papillomavirus 16 pseudovirions.** *J Virol* Aug. 2017, **91**, 16, <https://doi.org/10.1128/JVI.00307-17>.

49. Carse S, Lang D, Katz AA, Schäfer G: **Exogenous vimentin supplementation transiently Affects early Steps during HPV16 pseudovirus infection.** *Viruses* Dec. 2021, **13**, <https://doi.org/10.3390/v13122471>. 2471–2471.

This work demonstrates that application of exogenous vimentin can inhibit uptake of HPV pseudoviruses *in vitro* and modified the cell-surface binding interaction between HPV and heparan sulphate proteoglycan.

50. Zhang Y, *et al.*: **Host cytoskeletal vimentin serves as a structural organizer and an RNA-binding protein regulator to facilitate Zika viral replication.** *Proc Natl Acad Sci U S A* Feb. 2022, **119**, e2113909119, <https://doi.org/10.1073/pnas.2113909119>.

51. Turkki P, Laajala M, Flodström-Tullberg M, Marjomäki V: **Human enterovirus Group B viruses rely on vimentin dynamics for efficient processing of viral nonstructural proteins.** *J Virol* 2020, **94**, 2, <https://doi.org/10.1128/jvi.01393-19>.

52. Zhang J-M, *et al.*: **Quantitative analysis of the effects of vimentin intermediate filaments on the early stages of influenza A virus infection.** *New J Chem* Jun. 2023, <https://doi.org/10.1039/D3NJ00952A>.

53. Liu P, Zhang S, Ma J, Jin D, Qin Y, Chen M: **Vimentin inhibits α -tubulin acetylation via enhancing α -TAT1 degradation to suppress the replication of human parainfluenza virus type 3.** *PLoS Pathog* Sep. 2022, **18**, e1010856, <https://doi.org/10.1371/journal.ppat.1010856>.

54. Li Z, *et al.*: **A vimentin-targeting oral compound with host-directed antiviral and anti-inflammatory Actions Addresses Multiple Features of COVID-19 and related diseases.** *mBio* 2021, **12**, 5, <https://doi.org/10.1128/mBio.02542-21>.

This work demonstrated that the vimentin-targeting compound ALD-R491 shows therapeutic efficacy in a SARS-CoV-2 mouse infection model.

55. Adolf A, *et al.*: **Release of astroglial vimentin by extracellular vesicles: modulation of binding and internalization of C3 transferase in astrocytes and neurons.** *Glia* 2019, **67**:703–717, <https://doi.org/10.1002/glia.23566>.

56. Ostrowska-Podhorodecka Z, Ding I, Norouzi M, McCulloch CA: **Impact of vimentin on regulation of cell signaling and matrix remodeling.** *Front Cell Dev Biol* 2022, **10**:869069, <https://doi.org/10.3389/fcell.2022.869069>.

57. Lind SE, Smith DB, Janmey PA, Stossel TP: **Role of plasma gelsolin and the vitamin D-binding protein in clearing actin from the circulation.** *J Clin Invest* Sep. 1986, **78**: 736–742.