Available online at www.sciencedirect.com

ScienceDirect

Current Opinion in Cell Biology

Extracellular vimentin: Battle between the devil and the angel

Divyendu Goud Thalla[1] and Franziska Lautenschläger[1,2]

Abstract

Vimentin, an intracellular cytoskeletal protein, can be secreted by various cells in response to conditions such as injury, stress, senescence, and cancer.

Once vimentin is secreted outside of the cell, it is called extracellular vimentin. This extracellular vimentin is significantly involved in pathological conditions, particularly in the areas of viral infection, cancer, immune response, and wound healing. The effects of extracellular vimentin can be either positive or negative, for example it can enhance axonal repair but also mediates SARS-CoV-2 infection. In this review, we categorize the functional implications of extracellular vimentin based on its localization outside the cell. Specifically, we classify extracellular vimentin into two distinct forms: surface vimentin, which remains bound to the cell surface, and secreted vimentin, which refers to the free form that is completely released outside the cell. Overall, extracellular vimentin has a dual nature that encompasses both beneficial and detrimental effects on the functionality of cells, organs and whole organisms. Here, we summarize its effects in viral infection, cancer, immune response and wound healing. We find that surface vimentin is often associated with negative consequences, whereas secreted vimentin manifests predominantly with positive influences. We found that the observed effects of extracellular vimentin strongly depend on the specific circumstances under which its expression occurs in cells.

Addresses

[1] Experimental Physics, Saarland University, Saarbrücken, Germany
[2] Centre for Biophysics, Saarland University, Saarbrücken, Germany

Corresponding author: Lautenschläger, Franziska (f.lautenschlaeger@physik.uni-saarland.de)

Current Opinion in Cell Biology 2023, **85**:102265

This review comes from a themed issue on **Cell Architecture 2023**

Edited by **Patrick Lusk** and **John Eriksson**

For complete overview of the section, please refer the article collection - Cell Architecture 2023

Available online 29 October 2023

https://doi.org/10.1016/j.ceb.2023.102265

Introduction

Vimentin is a type III intermediate filament that is widely expressed in various cells, particularly those of mesenchymal origin [1]. As a component of the cytoskeleton, vimentin plays an important role in maintaining cell shape and integrity, facilitating cellular movement, and regulating intracellular signaling pathways [2,3]. Dysregulation of vimentin expression has been linked to several human diseases, including cancer, cardiovascular disorders, and neurodegenerative disorders, making it a promising therapeutic target [4–7].

In the past it was believed that vimentin, as an intracellular protein, was exclusively localized within the cytoplasm of cells. But emerging data suggests that vimentin can be secreted by various cell types, including fibroblasts, endothelial cells, and immune cells, such as macrophages [8]. The secretion of vimentin from these cells does occur in response to different stimuli, including stress, inflammation, senescence and injury [9–12]. Even though the exact mechanisms by which vimentin is secreted from cells are not fully understood, it has been proposed that vimentin can be secreted via a non-classical secretion pathway, such as exosome-mediated secretion and secretion induced by agents that disrupt classical secretion and membrane potential [13,14].

Independent of its secretion pathway, extracellular vimentin is believed to play a role in various physiological and pathological processes, such as wound healing, cancer, and inflammation Figure 1 [4,7,15,16].

One of the most well-known functions of extracellular vimentin is that it can trigger an immune response when it is released from damaged or stressed cells [17]. In this way, extracellular vimentin can contribute to inflammation and the recruitment of immune cells to the site of injury or infection. Extracellular vimentin can act as a danger signal, triggering an immune response to bacterial or viral infections [9,18]. However, it can also facilitate viral entry into cells, for example in the case of SARS-CoV-2, dengue virus 2 as well as human papillomavirus [19–21]. In addition to its role in the immune response, extracellular vimentin has been implicated in wound healing and tissue repair, as it can promote the migration and proliferation of fibroblasts [11,15]. There is also evidence that extracellular vimentin is involved in cancer progression and metastasis, as it can promote the invasion and migration of cancer cells [4,22,23].

Overall, the functions of extracellular vimentin are complex and multifaceted. So, we wonder if extracellular vimentin is rather beneficial or detrimental for organisms? In this review, we discuss the positive and negative impact of extracellular vimentin, which is dependent on the context and the specific physiological or pathological process involved.

Occurrence of extracellular vimentin

Since the outbreak of the SARS-CoV-2 pandemic and the discovery of the involvement of extracellular vimentin in its infection, the interest of the scientific community in extracellular vimentin has grown significantly on par with its intracellular counterpart.

Although the functional role of extracellular vimentin is still an active area of research with many unanswered questions, it is becoming increasingly clear that this protein is not simply a mis localized protein. Rather, extracellular vimentin has the potential to play various roles in different physiological and pathological processes. Understanding how vimentin is released from cells, its organization outside of the cell, as well as its interaction with surrounding cells will improve our understanding of the way extracellular vimentin affects different physiological and pathological processes.

Extracellular vimentin generally exists in two primary forms: one that is anchored to the outer surface of cells and another one that is released into the extracellular space Figure 1.

Surface vimentin

Surface vimentin refers to the form of vimentin that remains bound to the cell surface during its secretion process (Figure 1). The surface vimentin acts primarily as a receptor or co-receptor on the cell surface, interacting with other proteins such as Angiotensin-converting enzyme 2 [24,25] and influencing the behaviour of the cell it is located on (Figure 2a).

Secreted vimentin

When vimentin is fully secreted into the extracellular matrix and is no longer bound to the cell surface, it is called secreted vimentin. Once secreted, vimentin acts as an effector protein by binding to various receptors such as Insulin like growth factor 1 receptor (promotes axonal growth), Dectin-1(activates Dectin-1), CD44 (can replace CD443MUT) on corresponding cells and exerting an influence on their behaviour (Figure 2b) [15,17,18,26].

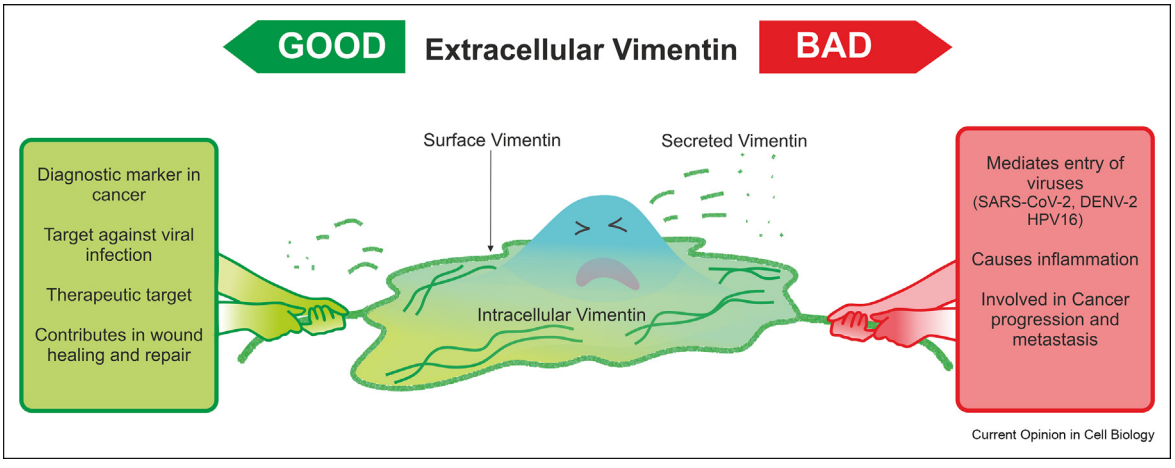
Implications of extracellular vimentin in health and disease

Extracellular vimentin exerts a substantial influence on numerous conditions in healthy and pathological conditions. Here, we summarize its effects in bacterial and viral infections, cancer, immune response and wound healing.

Bacterial and viral infections

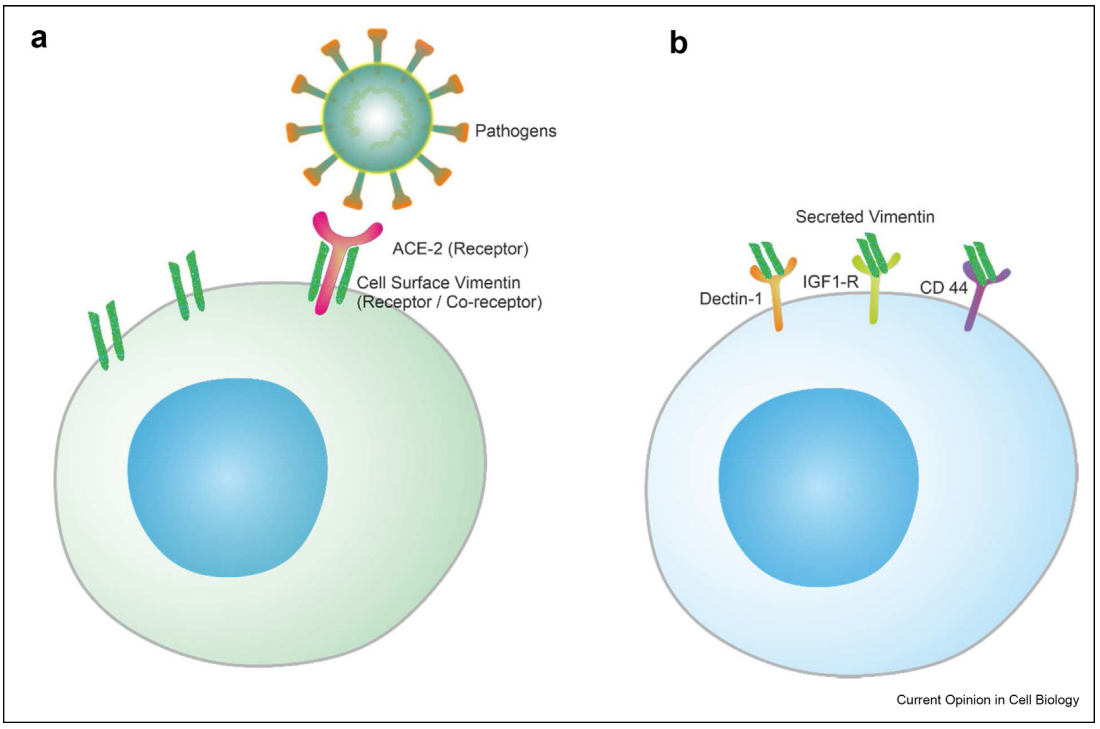
Surface vimentin can act as an attachment factor that helps the pathogen to find its true receptor, facilitating their attachment to the cell surface. It can also interact with host cell receptors to form a complex that promotes their entry. It facilitates the entry of bacteria such as *E. coli* K1, Group B Streptococcus, Listeria monocytogenes, Propionibacterium acnes, Mycobacterium avium subspecies hominissuis, Shigella flexneri and E. coli [27]. Surface vimentin meditates the infection potential of viruses

Figure 1



Schematic illustrating the diverse roles of extracellular vimentin.

Figure 2



Schematic representing the distinct forms of extracellular vimentin. a) Surface vimentin acts as a receptor or co-receptor for multiple pathogens. b) Secreted vimentin can bind directly to receptors of cells.

such as Chandipura vesiculovirus, Dengue Virus 2, Human Papillomavirus Type 16, SARS-CoV-2 [19,20,28,29].

On the other hand, when the secreted form of vimentin directly binds to the viral particles first, it inhibits the viral uptake. For example, the pre-incubation of HPV16-PsVs (pseudoviruses) with recombinant vimentin has been shown to delay viral internalization at early stages [21]*.

Altogether, these findings present an opportunity to target extracellular vimentin as a potential strategy for inhibiting the entry of viruses. A recent study demonstrated that administering hzVSF-v13, a humanized monoclonal antibody targeting extracellular vimentin, through intravenous injection in SARS-CoV-2-infected roborovski SH101 hamsters, effectively treated COVID-19. The treatment suppressed inflammation and viral replication by reducing extracellular vimentin in the blood. The study found that the therapeutic efficacy of this antibody was better than that of Remdesivir, a commonly used antiviral medication [30]. Additionally, a previous study had shown that targeting vimentin on the cell surface with pritumumab, a human monoclonal antibody, could inhibit the internalization of SARS-CoV-2 pseudo virus [31]*. These results suggest that targeting extracellular vimentin with monoclonal antibodies may be a promising approach to treating COVID-19 and warrant further investigation.

Cancer

Surface vimentin is found on various cancer cells. Particularly, it is used as a marker for circulating tumour cells (CTCs). CTCs are cancer cells that have detached from a primary tumour and entered the bloodstream, where they circulate throughout the body. CTCs can be detected in the blood of patients with many different types of cancers including lung cancer, gastric cancer, and neuroblastoma [32,33]. Further, their presence may indicate the spread of the cancer to other parts of the body.

Lung cancer

CTCs positive for cell surface vimentin (CSV^{+}) have been suggested as a viable biomarker for the detection of lung cancer. They have a positive correlation with lymph node and distant metastases, indicating that they are found in a more aggressive subtype of CTCs [32].

Gastric cancer

A colocalization of programmed death-ligand 1 (PD-L1) and CSV has been identified in locally advanced gastric cancer) tumour specimens. Knocking down PD-L1 led to

a decrease in CSV expression in gastric cancer cell lines. A higher number of CSV^+ $PD\text{-}L1^+$ CTCs correlates with shorter survival and poor response to therapy. Thus, using a CSV-constituted method to detect $PD\text{-}L1^+$ CTCs could serve as a marker for gastric cancer [33].

Neuroblastoma

In a recent study on neuroblastoma patients [34], researchers identified CSV as a marker for CTCs. CSV-based CTC detection was found to be a highly sensitive method for predicting disease relapse. Patients who had no detectable CSV^+ CTCs had a significantly better prognosis and longer overall survival. Conversely, those who had a high number of CSV^+ CTCs required more cycles of therapy to prevent disease relapse. These findings suggest that CSV-based CTC detection could be a useful tool for monitoring disease progression and informing treatment decisions for neuroblastoma patients [34]**.

Collectively, the presence of CSV protein on the surface of CTCs serves as a valuable marker for selectively capturing and isolating them from blood samples, making it an excellent diagnostic tool for assessing cancer progression. A recent study successfully achieved an antagonistic effect on non-small cell lung cancer cells by optimizing a peptide that binds to the cell surface protein vimentin. This promising approach holds the potential for developing new and more effective treatments [35].

In addition to this role in the diagnosis of cancer, the secreted form of vimentin also plays a role in cancer progression and metastasis. We and others found that it promotes cancer cell migration and invasion by interacting with the cell surface receptors [22,36]. Furthermore, secreted vimentin plays an active role in angiogenesis, the process by which new blood vessels are formed to supply nutrients and oxygen to tumours [14]. Interestingly, vaccines are now being developed to target extracellular vimentin to treat cancer. For example, a recent study has demonstrated that immunization with a Montanide ISA 720/CpG vaccine targeting extracellular vimentin effectively triggers a robust humoral immune response and impedes tumour growth in mice [37]**.

Immune system

Extracellular vimentin has been, mostly in its secreted form, shown to play a role in the immune system. It can act as a danger signal and activate immune cells such as macrophages and dendritic cells [9,38]. Moreover, extracellular vimentin can act as an autoantigen and trigger autoimmune responses. Antibodies against extracellular vimentin have been found in patients with various autoimmune diseases, including rheumatoid arthritis and systemic lupus erythematosus [39–41].

In the following are a few examples of immune cells that have been reported to express extracellular vimentin.

Neutrophils

Neutrophils are white blood cells differentiated from granulocytes. They play a critical role in the immune response to infections. There is evidence that neutrophils can release extracellular vimentin in response to certain stimuli, and that this may contribute to the formation of neutrophil extracellular traps, which are web-like structures that can capture and kill invading pathogens [42].

Macrophages

Macrophages are another type of white blood cells derived from monocytes. They are involved in the immune response after infections. Macrophages have been reported to express extracellular vimentin in certain contexts, such as during the development of atherosclerosis, a condition in which fatty deposits build up in the arteries. In this context, extracellular vimentin induces the production of pro-inflammatory cytokines, such as IL-6, and TNF-α [10]. Further, we have recently shown that the addition of extracellular vimentin enhances the migration and phagocytosis capacity of macrophages [43]*.

Dendritic cells

Dendritic cells belong to immune cell that play a crucial role in the initiation of an immune response. Extracellular vimentin has been shown to have a dual effect on cytokine secretion by dendritic cells. It can decrease the production of pro-inflammatory cytokines such as IL-6 and IL-12, while increasing the secretion of the anti-inflammatory cytokine IL-10. Therefore, it appears that extracellular vimentin could have an inhibitory effect on pro-inflammatory adaptive immune responses. Its presence may help to prevent tissue damage, thereby significantly reducing the risk of autoimmune diseases [38].

Overall, extracellular vimentin plays a complex role in immune function, both promoting and inhibiting inflammation depending on the specific context. Its involvement in autoimmune diseases suggests that it may be a potential therapeutic target for these conditions.

Wound healing

Secreted extracellular vimentin has been found to play a role in wound healing. In response to tissue injury, cells release extracellular vimentin, which regulates various aspects of the wound healing process, including inflammation, cell migration, and tissue remodelling. For instance, it has been demonstrated that extracellular vimentin promotes the migration of fibroblasts, which are essential for generating the extracellular matrix and facilitating tissue remodelling during wound healing

[36]. Furthermore, addition of extracellular vimentin to endothelial cells promotes a pro-migratory phenotype and enhances migration of individual cells [14].

In another study, astrocyte-secreted vimentin enhanced axonal growth *in vitro* and consequently promoted functional recovery in spinal cord injured mice [15,44]. In a cataract surgery model, it was shown that vimentin is released upon injury and binds to the mesenchymal leader cells located at the wound edge. This binding event facilitates a transition of these cells to a myofibroblast phenotype, which promotes wound closure [11].

Not only secreted extracellular vimentin, but also surface viementin promotes wound healing. This can be used for example in approaches like gene therapy. For instance, in the treatment of fibrosis, it is crucial to target myofibroblast and activated stellate cells. These cells do express surface vimentin. Therefore, these cells can be detected by targeting vimentin using polymer-conjugated polyethyleneimine linked to N-acetylglucosamine to deliver oligonucleotides [45].

Summing up, extracellular vimentin appears to be an important player in both tissue repair and wound healing.

Conclusions and future directions

Here, we describe the known aspects of extracellular vimentin in relation to four broad categories of physiological and pathological processes: cancer, viral infections, immune responses, and wound healing. The discovery of the substantial involvement of extracellular vimentin in the regulation of these processes is not only of interest to the Intermediate Filaments community but also to a wider audience, up to clinicians working on theses pathogenic conditions. In this review, we highlight how the presence of extracellular vimentin, whether on the cell surface or freely expressed, differentially impacts these aspects.

In viral infections, surface vimentin facilitates the entry of viral particles into cells, while secreted vimentin can interfere viral infection by directly binding to viral particles. Conversely, in the context of cancer, surface vimentin can serve as a diagnostic marker, aiding in cancer diagnosis. However, secreted vimentin promotes cancer cell migration, invasion, and angiogenesis, ultimately having a negative impact on the patients. In the context of immune response and wound healing, secreted vimentin assumes a significant role. It possesses the ability to either promote or inhibit inflammation, depending on the specific context, while also actively facilitating wound healing and tissue repair.

Overall, extracellular vimentin exhibits a dual nature, encompassing both positive and negative effects. Surface vimentin tends to lean more towards the negative aspects, while secreted vimentin predominantly manifests positive effects. But these also depend on circumstances in which extracellular vimentin is exhibited by the cells.

To modulate the secretion of vimentin for specific purposes, it is crucial to understand the mechanism underlying its secretion. In a recent study, we proposed that activated macrophages secrete vimentin in the form of small fragments, demonstrating polarization on the surface [43]. In addition, there are reports showing that a transition from the filamentous form to the multimer conformation is required for expression on the cell surface for type III intermediate filaments in general [46].

In future work, we and others should aim to identify the precise vimentin secretion pathway. One hypothesis is the potential involvement of microtubules. It is now recognized that vimentin interacts with and serves as template for microtubules within the cell, facilitating its transportation to the cell periphery [47]. It is likely that microtubules may also influence the transport of vimentin to the extracellular space. By studying the role of microtubules in vimentin secretion, we can unveil a secretion pathway for vimentin that holds immense potential for treating various diseases and combating viral infections.

Disclosure instructions

During the preparation of this work, we used ChatGPT in order to improve our sentences. After using this tool, we reviewed and edited the content as needed and take full responsibility for the content of the publication.

Author contribution

Conceptualization and writing: DT and FL; visualization: DT; supervision and funding acquisition: FL.

Funding

This work was supported by DFG (SFB1027 project A10).

Declaration of competing interest

The author declares that they have no known competing financial interests or personal relationships that could, have influenced the work reported in this paper.

Data availability

Review.

Acknowledgments

We would like to express our sincere gratitude to Galia Magela Montalvo Bereau and Ramona Grünewald for their invaluable contributions in proofreading the manuscript and providing valuable feedback.

References

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

* of special interest
** of outstanding interest

1. Eriksson JE, *et al.*: **Introducing intermediate filaments: from discovery to disease**. *J Clin Investig* 2009, **119**:1763–1771.
2. Ivaska J, *et al.*: **Novel functions of vimentin in cell adhesion, migration, and signaling**. *Exp Cell Res* 2007, **313**:2050–2062.
3. Danielsson F, *et al.*: **Vimentin diversity in health and disease**. *Cells* 2018, **7**:147.
4. Satelli A, Li S: **Vimentin in cancer and its potential as a molecular target for cancer therapy**. *Cell Mol Life Sci* 2011, **68**: 3033–3046.
5. Ridge KM, *et al.*: **Roles of vimentin in health and disease**. *Gene Dev* 2022, **36**:391–407.
6. Xiao J, *et al.*: **Circulating vimentin is associated with future incidence of stroke in a population-based cohort study**. *Stroke* 2021, **52**:937–944.
7. Chen K-Z, *et al.*: **Vimentin as a potential target for diverse nervous system diseases**. *Neural Regeneration Research* 2023, **18**:969–975.
8. Patteson AE, *et al.*: **Mechanical and non-mechanical functions of filamentous and non-filamentous vimentin**. *Bioessays* 2020, **42**:2000078.
9. Mor-Vaknin N, *et al.*: **Vimentin is secreted by activated macrophages**. *Nat Cell Biol* 2003, **5**:59–63.
10. Kim S, *et al.*: **Oxidized LDL induces vimentin secretion by macrophages and contributes to atherosclerotic inflammation**. *J Mol Med* 2020, **98**:973–983.
11. Walker JL, *et al.*: **In wound repair vimentin mediates the transition of mesenchymal leader cells to a myofibroblast phenotype**. *Mol Biol Cell* 2018, **29**:1555–1570.
12. Frescas D, *et al.*: **Senescent cells expose and secrete an oxidized form of membrane-bound vimentin as revealed by a natural polyreactive antibody**. *Proc Natl Acad Sci USA* 2017, **114**:E1668–E1677.
13. Parvanian S, *et al.*: **Exosomal vimentin from adipocyte progenitors accelerates wound healing**. *Cytoskeleton* 2020, **77**: 399–413.
14. van Beijnum JR, *et al.*: **Extracellular vimentin mimics VEGF and is a target for anti-angiogenic immunotherapy**. *Nat Commun* 2022, **13**:2842.
15. Shigyo M, *et al.*: **Extracellular vimentin interacts with insulin-like growth factor 1 receptor to promote axonal growth**. *Sci Rep* 2015, **5**:12055.
16. Martinez-Vargas M, *et al.*: **A novel interaction between extracellular vimentin and fibrinogen in fibrin formation**. *Thromb Res* 2023, **221**:97–104.
17. Ramos I, *et al.*: **Vimentin as a multifaceted player and potential therapeutic target in viral infections**. *Int J Mol Sci* 2020, **21**: 4675.
18. Thiagarajan PS, *et al.*: **Vimentin is an endogenous ligand for the pattern recognition receptor Dectin-1**. *Cardiovasc Res* 2013, **99**:494–504.
19. Amraei R, *et al.*: **Extracellular vimentin is an attachment factor that facilitates SARS-CoV-2 entry into human endothelial cells**. *Proc Natl Acad Sci USA* 2022, **119**, e2113874119.
20. Yang J, *et al.*: **Superficial vimentin mediates DENV-2 infection of vascular endothelial cells**. *Sci Rep* 2016, **6**:38372.
21. * Carse S, *et al.*: **Exogenous vimentin supplementation transiently affects early steps during HPV16 pseudovirus infection**. *Viruses* 2021, **13**.
This work demonstrates how extracellular vimentin can be used to interfere with the internalization of viral particles.
22. Thalla DG, *et al.*: **Role of extracellular vimentin in cancer-cell functionality and its influence on cell monolayer permeability changes induced by SARS-CoV-2 receptor binding domain**. *Int J Mol Sci* 2021, **22**:7469.
23. Satelli A, *et al.*: **Potential function of exogenous vimentin on the activation of wnt signaling pathway in cancer cells**. *J Cancer* 2016, **7**:1824–1832.
24. Arrindell J, *et al.*: **Vimentin is an important ACE2 co-receptor for SARS-CoV-2 in epithelial cells**. *iScience* 2022, **25**:105463.
25. Lalioti V, *et al.*: **Immunolocalization studies of vimentin and ACE2 on the surface of cells exposed to SARS-CoV-2 Spike proteins**. *bioRxiv* 2021:2021. 05.04.442648.
26. Päll T, *et al.*: **Soluble CD44 interacts with intermediate filament protein vimentin on endothelial cell surface**. *PLoS One* 2011, **6**, e29305.
27. Miao C, *et al.*: **The diverse actions of cytoskeletal vimentin in bacterial infection and host defense**. *J Cell Sci* 2023, **136**.
28. Schäfer G, *et al.*: **Vimentin modulates infectious internalization of human papillomavirus 16 pseudovirions**. *J Virol* 2017, **91**:e00307–e00317.
29. Kavathekar VK, *et al.*: **Role of cell surface vimentin in Chandipura virus replication in Neuro-2a cells**. *Virus Res* 2020, **285**: 198014.
30. Kim H-M, *et al.*: *Removal of extracellular vimentin in blood confers resistance to viral infection*. Research Square; 2022.
31. * Suprewicz Ł, *et al.*: **Extracellular vimentin as a target against SARS-CoV-2 host cell invasion**. *Small* 2022, **18**:2105640.
This work is amongst the first to target extracellular vimentin using antibodies for treating infections, such as COVID-19.
32. Xie X, *et al.*: **Evaluation of cell surface vimentin positive circulating tumor cells as a diagnostic biomarker for lung cancer**. *Front Oncol* 2021:11.
33. Liu M, *et al.*: **Prognostic significance of PD-L1 expression on cell-surface vimentin-positive circulating tumor cells in gastric cancer patients**. *Mol Oncol* 2020, **14**:865–881.
34. ** Batth IS, *et al.*: **Cell surface vimentin-positive circulating tumor cell-based relapse prediction in a long-term longitudinal study of postremission neuroblastoma patients**. *Int J Cancer* 2020, **147**:3550–3559.
This work is amongst the first to demonstrate how CSV based detection of CTCs can be used to predict relapse in neuroblastoma patients.
35. Zhang H, Gomika Udugamasooriya D: **Optimization of a cell surface vimentin binding peptoid to extract antagonist effect on lung cancer cells**. *Bioorg Chem* 2022, **129**:106113.
36. Bucki R, *et al.*: **Extracellular vimentin is sufficient to promote cell attachment, spreading, and motility by a mechanism involving N-acetyl glucosamine-containing structures**. *bioRxiv* 2022:2022. 11.28.518249.
37. ** van Loon K, *et al.*: **Cancer vaccination against extracellular vimentin efficiently adjuvanted with Montanide ISA 720/CpG**. *Cancers* 2022, **14**:2593.
This study showcases a new approach of generating vaccines against extracellular vimentin to treat cancer.
38. Yu, M.B., et al., Extracellular vimentin modulates human dendritic cell activation. (1872-9142 (Electronic)).
39. Van Steendam K, *et al.*: **Citrullinated vimentin as an important antigen in immune complexes from synovial fluid of rheumatoid arthritis patients with antibodies against citrullinated proteins**. *Arthritis Res Ther* 2010, **12**:R132.

40. Li Y, *et al.*: **Antibodies against carbamylated vimentin exist in systemic lupus erythematosus and correlate with disease activity**. *Lupus* 2020, **29**:239–247.

41. Shindo S, *et al.*: **Extracellular release of citrullinated vimentin directly acts on osteoclasts to promote bone resorption in a mouse model of periodontitis**. *Cells* 2023, **12**:1109.

42. Thiam HR, *et al.*: **NETosis proceeds by cytoskeleton and endomembrane disassembly and PAD4-mediated chromatin decondensation and nuclear envelope rupture**. *Proc Natl Acad Sci USA* 2020, **117**:7326–7337.

43. * Thalla DG, *et al.*: **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**.
This is the first study which shows vimentin is secreted from back of activated macrophages in a polarized manner.

44. Teshigawara K, *et al.*: **A novel compound, denosomin, ameliorates spinal cord injury via axonal growth associated with astrocyte-secreted vimentin**. *Br J Pharmacol* 2013, **168**:903–919.

45. Song I, Ise H: **Development of a gene delivery system of oligonucleotides for fibroses by targeting cell-surface vimentin-expressing cells with N-Acetylglucosamine-Bearing polymer-conjugated polyethyleneimine**. *Polymers* 2020, **12**:1508.

46. Hwang B, Ise H: **Multimeric conformation of type III intermediate filaments but not the filamentous conformation exhibits high affinity to lipid bilayers**. *Gene Cell* 2020, **25**:413–426.

47. Gan Z, *et al.*: **Vimentin intermediate filaments template microtubule networks to enhance persistence in cell polarity and directed migration**. *Cell Systems* 2016, **3**:252–263.e8.