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Vimentin in the tumor microenvironment: orchestrating invasion, immunity, and metabolism

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ABSTRACT

Vimentin, a type III intermediate filament protein, has gained recognition as a multifunctional regulator within the tumor microenvironment (TME). While traditionally considered a hallmark of epithelial-to-mesenchymal transition (EMT), vimentin is increasingly understood as a structural and signaling hub essential for the functional complexity of mesoderm-derived and EMT-transitioned cells. It bridges cytoskeletal architecture with key signaling networks, linking cellular plasticity to mechanotransduction, immune modulation, and metabolic regulation. This unique versatility underlies vimentin's essential role in supporting the migratory, remodeling, and adaptive behaviors required in contexts such as wound healing, inflammation, and tissue remodeling—capabilities that cancer cells have co-opted to their advantage. Indeed, vimentin's pervasive expression across aggressive cancers reflects its ability to scaffold and coordinate the cytoskeletal and signaling rewiring needed for malignancy. This review provides an integrated overview of vimentin's diverse roles in the TME, emphasizing its contributions to tumor invasiveness, immune regulation, and metabolic adaptation. We conclude by discussing how these insights may inform the development of vimentin-centered strategies to improve therapeutic outcomes in cancer.

1. Introduction

Intermediate filaments (IFs) are a critical component of the cytoskeleton, providing structural support, mechanical resilience, and spatial organization to cells (Coelho-Rato et al., 2024b). Among the diverse family of IF proteins, vimentin is the most widely expressed type III intermediate filament, predominantly found in mesenchymal cells. Beyond its canonical role as a cytoskeletal scaffold, vimentin is increasingly recognized as a dynamic regulator of various cellular processes, including migration, adhesion, signal transduction, and organelle positioning (Ridge et al., 2022).

Vimentin has been featured as a key player in various stages of wound healing, coordinating fibroblast proliferation and migration, epithelial-to-mesenchymal transition (EMT) of keratinocytes, and tissue remodeling (Parvanian et al., 2025; Cheng et al., 2016; Coelho-Rato et al., 2024a). This is particularly relevant given the widely recognized notion that *cancer resembles "a wound that never heals"*, a concept first articulated by Harold Dvorak (Dvorak, 1986). In this context, vimentin should not be viewed merely as a passive marker of EMT, but rather as an active integrator of signaling and structural plasticity that supports both wound repair and tumor progression. Its prominent association with EMT, a cancer-related process that mirrors key aspects of wound repair, underscores its central role in tumor progression. During EMT, epithelial cells lose junctional proteins such as E-cadherin and gain mesenchymal markers including vimentin, fibronectin, and N-cadherin (Haerinck et al., 2023; Rato et al., 2024; Youssef and Nieto, 2024). Vimentin is not only a hallmark but also a functional driver of EMT plasticity, modulating cytoskeletal dynamics, focal adhesion turnover, and extracellular matrix remodeling. Its expression correlates with enhanced metastatic potential and poor clinical outcomes in several cancer types, including breast, prostate, colorectal, and lung carcinomas (Usman et al., 2021). The tumor microenvironment (TME) is a dynamic and heterogeneous ecosystem composed of cancer cells, stromal cells, immune cells, and extracellular matrix components (Anderson and Simon, 2020). Recent studies have shown that vimentin is actively involved in controlling interactions within the TME. Its upregulation is closely associated with EMT, enhanced migratory capacity, immune modulation, and metabolic reprogramming of tumor cells (Parvanian

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et al., 2025, 2023b; Glassy, 2025; Tabatabaee et al., 2024).

While initially considered a tumor cell-intrinsic marker, vimentin has now emerged as a multifaceted regulator within the TME (Tabatabaee et al., 2024). Vimentin expression is often elevated not only in invasive tumor cells but also in activated fibroblasts, including cancer-associated fibroblasts (CAFs), tumor-associated macrophages (TAMs), and endothelial cells undergoing angiogenesis (Dave and Bayless, 2014; Larionova et al., 2020; Nurmik et al., 2020). Furthermore, vimentin has been detected in extracellular vesicles (EVs) and even on the cell surface, implicating it in intercellular communication and immune modulation (Adolf et al., 2019; Bucki et al., 2022.; Fasipe et al., 2018; Martinez-Vargas et al., 2023; Parvanian et al., 2020, 2021, 2023a, 2023b; Shigyo et al., 2015; Shigyo and Tohda, 2016; Suprewicz et al., 2021, 2024; Thalla et al., 2022; van Beijnum et al., 2022; Yu et al., 2018). Its structural plasticity and diverse subcellular localizations enable vimentin to act as a central integrator of biomechanical and biochemical signals within the TME.

Given this broad functional spectrum, vimentin is now being explored not only as a biomarker but also as a therapeutic target. This review synthesizes current knowledge on the role of vimentin in the tumor microenvironment, focusing on its contributions to invasion, immune modulation, and metabolic adaptation (Fig. 1). To unify these diverse roles, we propose a conceptual model in which vimentin acts as a structural and signaling integrator, enabling cancer and stromal cells to dynamically adapt to mechanical, immune, and metabolic pressures within the tumor microenvironment. This framework positions vimentin as a central coordinator of adaptive plasticity, which supports tumor progression and resistance to therapy, and highlights its significance as a promising therapeutic target in cancer.

2. Vimentin and tumor invasion

2.1. Role in EMT and cytoskeletal remodeling

Vimentin is a 54 kDa type III intermediate-filament protein composed of a central α-helical rod domain flanked by intrinsically disordered head and tail regions. Two monomers align in parallel to form coiled-coil dimers, which then associate antiparallelly into staggered tetramers. Eight tetramers laterally assemble into ~60 nm unit-length filaments that elongate and anneal end-to-end to generate mature vimentin fibers. This hierarchical organization provides both mechanical resilience and dynamic flexibility, enabling rapid remodeling during processes such as migration, adhesion turnover, and cytokinetic reorganization (Eibauer et al., 2024) (Fig. 2).

Vimentin is not merely a bystander in EMT but a key effector. Its expression is directly regulated by EMT-inducing transcription factors such as Snail, Slug, Twist, and Zeb1/2, which are upregulated in response to TGF-β, Wnt, and hypoxia-inducible signaling pathways (Cheng et al., 2016; Lamouille et al., 2014).

Functionally, vimentin contributes to the dismantling of apical–basal polarity and the restructuring of the cytoskeleton. Unlike actin filaments and microtubules, vimentin intermediate filaments form a dynamic, cage-like network around the nucleus and extend toward the cell periphery, where they interact with actin stress fibers and microtubules. These interactions facilitate cell elongation, front–rear polarity, and directional migration, key hallmarks of invasive behavior Usman et al., (2021)). Vimentin filaments also enhance nuclear plasticity, enabling cancer cells to deform and traverse dense extracellular matrices during metastasis (Patteson et al., 2019).

Importantly, Virtakoivu et al. (Virtakoivu et al., 2015) demonstrated that ectopic expression of vimentin alone is sufficient to induce EMT in epithelial cancer cells, leading to loss of E-cadherin, gain of mesenchymal markers, and increased invasiveness independent of upstream transcriptional drivers. They further showed that vimentin physically regulates a Slug–ERK complex, stabilizing Slug and sustaining ERK signaling to reinforce EMT transcriptional programs. Vimentin carried by extracellular vesicles can also propagate EMT signaling, as discussed in the section on extracellular vimentin. This finding underscores that vimentin is not just a downstream marker of EMT but can actively initiate and sustain the transition through direct regulation of key

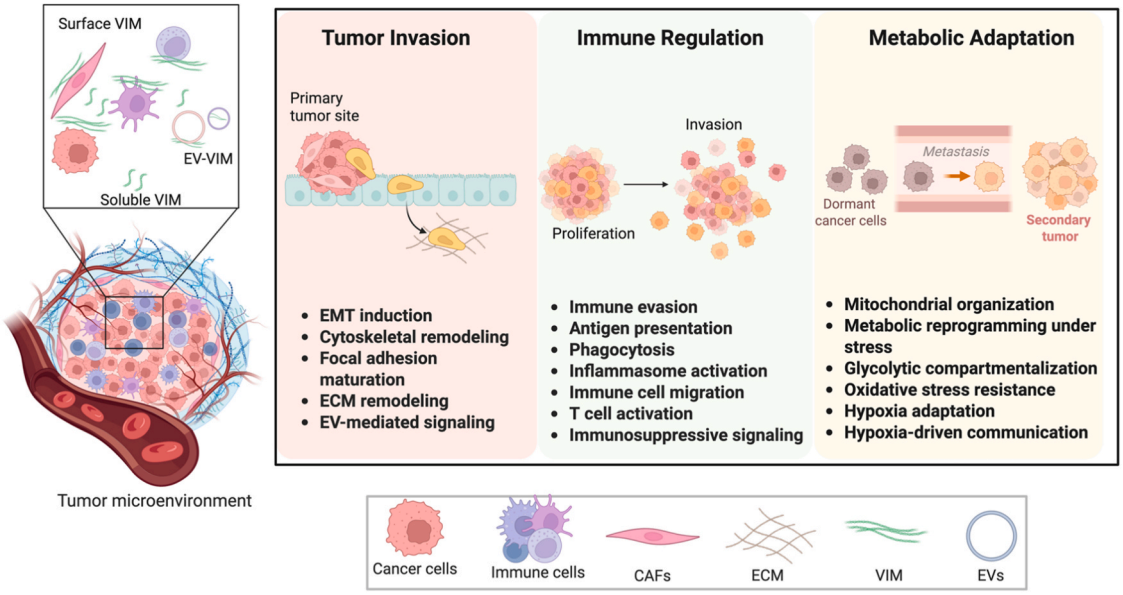

Fig. 1. Multifaceted roles of vimentin in the tumor microenvironment (TME). This schematic illustrates the diverse functional contributions of vimentin across tumor and stromal compartments in the TME. Vimentin exists in multiple forms, soluble, surface-bound, and extracellular vesicle (EV)-associated and is expressed by cancer cells, cancer-associated fibroblasts (CAFs), and immune cells. Left panel shows vimentin localization within the TME, including surface vimentin, soluble cytoplasmic pools, and EV-bound vimentin. Right panel outlines vimentin's contributions to: Tumor invasion, including EMT induction, cytoskeletal remodeling, focal adhesion maturation, ECM remodeling, and EV-mediated signaling; Immune regulation, including immune evasion, antigen presentation, phagocytosis, inflammasome activation, immune cell migration, T cell activation, and immunosuppressive signaling; Metabolic adaptation, including mitochondrial organization, metabolic reprogramming under stress, glycolytic compartmentalization, oxidative stress resistance, hypoxia adaptation, and hypoxia-driven intercellular communication. Bottom icons represent the key cell types and structural components within the TME contributing to or influenced by vimentin activity.

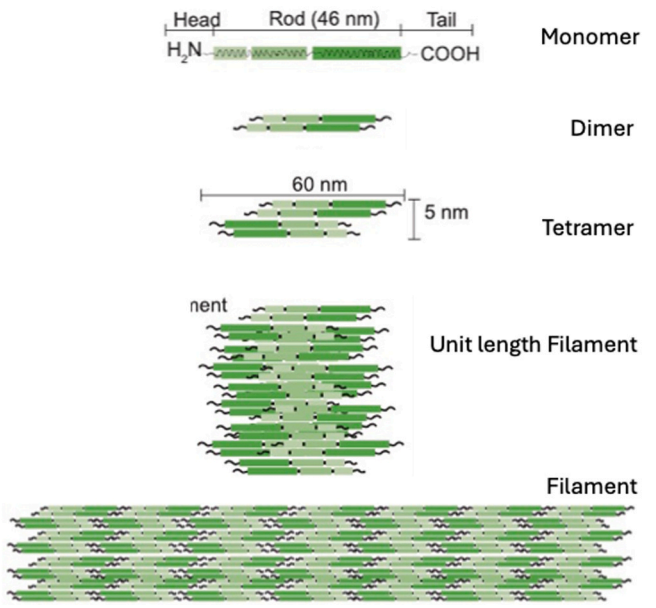

Fig. 2. Hierarchical assembly of vimentin intermediate filaments. Vimentin is a 54 kDa intermediate filament protein comprising an N-terminal head, a central α-helical rod domain (~46 nm), and a C-terminal tail. Two monomers align in parallel to form a coiled-coil dimer. Two dimers associate in an antiparallel, half-staggered configuration to form a non-polar tetramer, the soluble assembly unit. Eight tetramers laterally associate to generate a ~60 nm unit-length filament (ULF). Longitudinal annealing and radial compaction of ULFs produce mature ~10–12 nm filaments that constitute the dynamic vimentin network characteristic of mesenchymal cells.

signaling modules.

Knockdown or pharmacological inhibition of vimentin results in reduced cell migration, impaired invadopodia formation, and lower metastatic potential in multiple cancer models, including breast, prostate, and pancreatic carcinomas. These findings underscore vimentin's active role in cytoskeletal remodeling and mechanical adaptation during tumor cell invasion (Battaglia et al., 2018; Karoii et al., 2022; Lamouille et al., 2014; Leduc and Etienne-Manneville, 2015; Y. Li et al., 2025; Sherapura et al., 2025). In tumor cells, vimentin upregulation drives EMT and invasion, while in stromal CAFs, it supports ECM remodeling and the creation of a pro-invasive matrix architecture.

2.2. 00F0ocal adhesion and ECM interactions

Vimentin plays a crucial role in regulating focal adhesions, multiprotein complexes that anchor the cytoskeleton to the extracellular matrix (ECM) and mediate mechanotransduction. Vimentin IFs physically associate with focal adhesion complexes via linker proteins such as plectin and filamin A, stabilizing the adhesion structures and promoting their maturation (Alisafaei et al., 2024; Ostrowska-Podhorodecka and McCulloch, 2021).

Through interactions with integrins and adaptor proteins such as focal adhesion kinase (FAK), vimentin facilitates integrin recycling and spatial coordination of adhesion sites. This coordination supports the generation of traction forces and efficient forward translocation on both 2D and 3D matrices. The absence of vimentin impairs integrin-dependent adhesion dynamics, FAK activation, and ECM degradation—processes that are essential for the invasive behavior of EMT-transitioned cells (Shao et al., 2023; Zholudeva et al., 2024).Additionally, vimentin contributes to ECM remodeling by regulating the expression and activity of matrix metalloproteinases (MMPs), particularly MMP-2 and MMP-9. These enzymes degrade basement membrane components, clearing paths for migrating tumor cells. Vimentin-expressing cancer-associated fibroblasts (CAFs) also secrete ECM proteins such as fibronectin and tenascin C, establishing a pro-invasive matrix architecture that facilitates tumor cell dissemination (Ho Thanh et al., 2024; Ostrowska-Podhorodecka et al., 2022).

2.3. Extracellular vesicles and invasion-associated cargo

Vimentin has been detected both on the surface and inside EVs derived from tumor cells and stromal cells (Adolf et al., 2019; Bucki et al., 2022; Fasipe et al., 2018; Martinez-Vargas et al., 2023; Parvanian et al., 2020, 2021, 2023a, 2023b; Shigyo et al., 2015; Shigyo and Tohda, 2016; Suprewicz et al., 2021, 2024; Thalla et al., 2022; van Beijnum et al., 2022; Yu et al., 2018). Recent studies demonstrate that vimentin-bearing EVs act as potent mediators of intercellular communication within the tumor microenvironment, capable of inducing EMT in recipient epithelial cells through downregulation of E-cadherin and upregulation of mesenchymal markers such as N-cadherin and fibronectin (Fig. 3) (Parvanian et al., 2025).

Functionally, vimentin-enriched EVs carry invasion-associated cargo, including MMPs, integrins, EMT transcription factors, and miRNAs that regulate cytoskeletal dynamics and extracellular matrix degradation. Their uptake by recipient epithelial or stromal cells promotes a pro-invasive phenotype through horizontal transfer of bioactive molecules (Cheytan et al., 2025; Y. Zhang, Wang, et al., 2024). Mechanistically, these vesicles activate canonical EMT signaling pathways, such as TGF-β and the Wnt/β-catenin pathway, underscoring a signaling role for EV-associated vimentin beyond its structural transport function. Moreover, vimentin-containing EVs contribute to pre-metastatic niche formation by educating distant stromal cells and modulating vascular permeability, thereby facilitating metastatic colonization (Booijink et al., 2024). This EV-mediated mechanism complements the

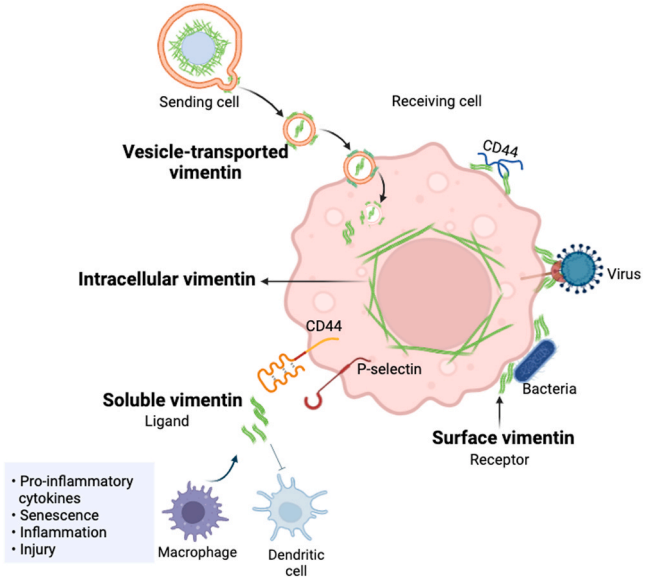

Fig. 3. Diverse localizations and signaling roles of intracellular and extracellular vimentin. Vimentin is dynamically distributed across intracellular, vesicular, and extracellular compartments. Intracellular vimentin filaments provide structural support and organize signaling complexes within the cytoplasm. During stress, injury, or cellular activation, vimentin is released either as soluble protein or within extracellular vesicles such as exosomes, which can be transferred between cells. Soluble vimentin acts as a ligand binding to CD44 and P-selectin on immune cells, promoting activation of macrophages and dendritic cells, which in turn secrete pro-inflammatory cytokines and amplify local inflammatory responses. On the plasma membrane, surface-associated vimentin functions as a receptor or co-receptor, facilitating the attachment and entry of viruses and bacteria. Through these complementary intracellular, vesicular, and extracellular roles, vimentin integrates structural remodeling with immune activation and pathogen recognition.

cell-intrinsic EMT and adhesion functions of vimentin, reinforcing its role as a structural and signaling integrator within the tumor microenvironment.

3. Vimentin in immune regulation

The tumor microenvironment (TME) is profoundly shaped by dynamic interactions between cancer cells and the immune system (Yuan et al., 2024). Vimentin plays an increasingly recognized role in this context, operating not only within tumor cells to facilitate immune evasion but also within immune cells to regulate key effector functions. Its contributions span a wide range of immunological processes, including surface-mediated immune evasion, antigen presentation, phagocytosis, cytokine release, and immune cell migration and adhesion. Vimentin is essential for the structural flexibility and signaling coordination required for immune cells to traffic through tissues and engage with tumors (Nieminen et al., 2006; Tabatabaee et al., 2024). This dual role, modulating immunity both from within cancer cells and through the cytoskeletal regulation of immune cell behavior, positions vimentin as a central integrator of immune dynamics within the TME.

3.1. Surface vimentin and immune evasion

Although vimentin is classically considered an intracellular protein, multiple studies have demonstrated its presence on the cell surface of various tumor types, activated lymphocytes, and endothelial cells. This ectopic localization is particularly relevant in cancer, where surface vimentin has been implicated in immune evasion (Glassy, 2025; Gu et al., 2024; M. Liu et al., 2020; Parvanian et al., 2023a, 2023b; Z. Yuan et al., 2025).

Surface vimentin can bind ligands such as NKp46, a natural killer (NK) cell receptor, and modulate NK cell-mediated cytotoxicity. In some cases, vimentin engagement with NK receptors can suppress immune responses, allowing tumor cells to escape immune surveillance (Garg et al., 2006). Moreover, surface vimentin has been shown to interact with pathogens and apoptotic cells, contributing to the formation of immune-privileged niches where tumor cells mimic apoptotic debris to avoid clearance (Müller et al., 2001; Starr et al., 2012; Thalla et al., 2022; Yao et al., 2016).

Importantly, vimentin is not only a target for immune evasion strategies by tumor cells but also plays a crucial role in regulating the behavior of immune cells themselves. Nieminen et al. (2006) demonstrated that vimentin is essential for lymphocyte adhesion and transcellular migration through endothelial barriers. In their study, vimentin-deficient lymphocytes exhibited impaired adhesion to endothelial cells and reduced capacity for diapedesis, revealing that vimentin contributes to the structural plasticity and mechanical resilience required for immune cell trafficking. The findings also suggest that vimentin regulates cytoskeletal dynamics at the rear of migrating lymphocytes, particularly in uropod formation, highlighting its role in directional migration and immune surveillance.

In the context of infection and inflammation, pathogens like *Listeria monocytogenes* and *Mycobacterium tuberculosis* exploit surface vimentin to facilitate entry into host cells, further underscoring its immunologically relevant roles (Bastounis et al., 2018; Suprewicz et al., 2024). While in cancer, this mimicry may support immune evasion, it also raises the possibility of targeting surface vimentin for therapeutic intervention or imaging (Gu et al., 2024; Y. Li et al., 2025; Z. Yuan et al., 2025).

3.2. Vimentin role in antigen presentation and phagocytosis

Vimentin influences the function and maturation of professional antigen-presenting cells (APCs), such as dendritic cells (DCs) and macrophages (Pereira et al., 2005; Thiagarajan et al., 2013). During immune activation, vimentin plays a role in endosomal trafficking, which is crucial for loading MHC class II antigens and presenting peptide-MHC complexes at the cell surface. Loss of vimentin has been associated with impaired endosome maturation and antigen cross-presentation, suggesting its importance in the priming of adaptive immune responses (Roghanian et al., 2010; Shaebani et al., 2022; Yu et al., 2018).

In macrophages, vimentin contributes to phagocytic cup formation, a process that relies on coordinated cytoskeletal remodeling. Vimentin filaments interface with actin networks to stabilize the plasma membrane and facilitate efficient engulfment of apoptotic cells or pathogens (Thalla et al., 2022). Additionally, vimentin is involved in the release of pro-inflammatory cytokines, such as IL-1β, through the regulation of the NLRP3 inflammasome, further linking it to immune activation and tumor inflammation (Alyaseer et al., 2020; Dos Santos et al., 2015).

Interestingly, extracellular vimentin has also been proposed to act as a damage-associated molecular pattern (DAMP) when released from dying or stressed cells, potentially triggering immune responses via pattern recognition receptors such as toll-like receptors (TLRs) (Suprewicz et al., 2025; van Loon et al., 2023).

3.3. Influence on immune cell migration and function

Vimentin is essential for immune cell migration, particularly under conditions that require rapid and adaptable cytoskeletal rearrangements (Arrindell and Desnues, 2023; van Loon et al., 2023). In lymphocytes, monocytes, neutrophils, and DCs, vimentin coordinates the structural flexibility needed to transmigrate through narrow endothelial gaps and ECM barriers (Håversen et al., 2018; Huynh et al., 2024). Vimentin-deficient leukocytes display impaired motility, reduced chemotaxis, and defective uropod formation, key features required for directional migration during immune surveillance or tumor infiltration (Da et al., n.d.; Nieminen et al., 2006; Stankevicins et al., 2019).

Furthermore, vimentin regulates T cell activation and polarization by influencing immune synapse formation and intracellular signaling cascades (Billadeau et al., 2007; D. Li et al., 2015). In activated T cells, vimentin relocalizes to the immune synapse, where it may scaffold signaling molecules such as ZAP-70 and Lck, thereby fine-tuning TCR signal strength (Brentville et al., 2016; Brown et al., 2001; Ma et al., 2024; Mastrogiovanni et al., 2020).

In the tumor context, vimentin expression in tumor-associated macrophages (TAMs) and myeloid-derived suppressor cells (MDSCs) correlates with immunosuppressive phenotypes. These vimentin-expressing cells can secrete immunomodulatory cytokines such as IL-10 and TGF-β, contributing to T cell exclusion and immune escape (Bai et al., 2024; Y. Zhang, Ding, et al., 2024). This section underscores vimentin's multifaceted role as a central integrator of immune regulation within both tumor and stromal compartments, in line with the unifying conceptual model.

Collectively, these findings illustrate the multifaceted role of vimentin in immune regulation. It modulates not only the structural aspects of immune cell movement but also key functional processes, such as antigen presentation, phagocytosis, and immune synapse signaling. Through these diverse mechanisms, vimentin shapes both innate and adaptive responses within the tumor microenvironment, emerging as a potential immunotherapeutic target.

4. Vimentin and metabolic adaptation

Metabolic reprogramming is a hallmark of cancer, enabling tumor cells to meet the energetic and biosynthetic demands of uncontrolled growth and survival in hostile microenvironments (Aden et al., 2024; Huang et al., 2025; Jiang et al., 2025; Liu et al., 2024). Traditionally viewed as a structural protein, vimentin has recently emerged as an important player in the metabolic flexibility of cancer cells. Through interactions with key organelles and signaling pathways, vimentin influences mitochondrial function, glycolysis, redox balance, and nutrient sensing, placing it at the intersection of cellular architecture and

metabolic regulation (Berr et al., 2023; Huynh et al., 2024; Lavenus et al., 2020; Mohanasundaram et al., 2022; Pérez-Sala and Quinlan, 2024; Satelli et al., 2016).

4.1. Vimentin–mitochondria interactions

One of the most intriguing aspects of vimentin's role in metabolism is its physical and functional association with mitochondria. Vimentin intermediate filaments form a perinuclear network that interfaces with mitochondrial membranes, influencing their spatial organization, trafficking, and morphology. This network plays a critical role in positioning mitochondria near regions of high ATP demand and in regulating mitochondrial fusion and fission dynamics (Chernoivanenko et al., 2015; Lee et al., 2024; Matveeva et al., 2010; Nekrasova et al., 2011; Tang et al., 2008).

Experimental studies have demonstrated that vimentin deficiency results in altered mitochondrial distribution, fragmentation, and reduced oxidative phosphorylation (OXPHOS) efficiency. For example, in vimentin-null fibroblasts, mitochondrial ATP production is impaired, and cells exhibit a compensatory increase in glycolysis, suggesting a metabolic shift toward the Warburg phenotype (Berr et al., 2023; Ding et al., 2021; Xuan et al., n.d.). These findings suggest that vimentin is crucial for maintaining optimal mitochondrial function and the metabolic plasticity necessary for cancer progression.

4.2. Glycolytic reprogramming and oxidative stress

Beyond its effect on mitochondria, vimentin also regulates glycolytic metabolism and the cellular redox state. Cancer cells undergoing EMT and cytoskeletal remodeling often shift toward increased glycolysis, a process in which vimentin has been shown to play a facilitative role (Pinho and Reis, 2015; Xu et al., 2024). Vimentin interacts with glycolytic enzymes such as aldolase A and phosphofructokinase, organizing them into metabolically active compartments that enhance local ATP production (Komura et al., 2012; Rho et al., 2009; Yang et al., 2023).

Furthermore, vimentin protects cancer cells from oxidative stress by modulating glutathione metabolism and buffering reactive oxygen species (ROS) (Berr et al., 2023; Q. F. Li et al., 2009; Matveeva et al., 2010; Pérez-Sala et al., 2015). Vimentin filaments act as a scaffold for NRF2, a key regulator of antioxidant defense supporting its nuclear translocation and transcriptional activity. In vimentin-depleted cells, oxidative stress accumulates, leading to increased sensitivity to chemotherapeutic agents and nutrient deprivation (Biskou et al., 2019; Håversen et al., 2018; Martínez-Cenalmor et al., 2024; Xiang et al., 2022).

These findings suggest that vimentin contributes to a pro-survival metabolic profile, enabling cancer cells to endure oxidative stress and adapt to fluctuating nutrient availability within the TME.

4.3. Crosstalk with hypoxia and HIF-1α

Hypoxia is a common feature of solid tumors, and vimentin plays a crucial role in enabling tumor cells to adapt to low-oxygen environments (Wilson and Hay, 2011). Under hypoxic conditions, the stabilization of HIF-1α drives the expression of genes that promote glycolysis, angiogenesis, and cell survival. Vimentin is among the HIF-1α target genes and is upregulated in response to hypoxia in various cancer types (Kidd et al., 2014; C. H. Li et al., 2017; W. Li et al., 2016; Lin et al., 2019; Zhu et al., 2016).

Importantly, vimentin not only responds to HIF-1α but also reinforces hypoxia signaling. It has been shown to interact with prolyl hydroxylases (PHDs), enzymes that regulate HIF-1α degradation. By sequestering or altering PHD localization, vimentin may contribute to sustained HIF-1α activity and the hypoxia-induced ge00ne expression program (Wang et al., 2011).

Additionally, vimentin-expressing cancer cells often produce extracellular vesicles enriched in hypoxia-responsive factors and metabolic enzymes, thereby promoting metabolic reprogramming in neighboring cells and supporting angiogenesis (Shamshiripour et al., 2024; van Beijnum et al., 2022; P. Zhang et al., 2021). These metabolic functions further illustrate vimentin's integrative role in orchestrating adaptation to metabolic stress in both tumor and stromal compartments within the TME.

Through its dynamic interactions with mitochondria, glycolytic enzymes, redox regulators, and hypoxia-inducible factors, vimentin helps drive the metabolic adaptability that is critical for tumor survival and progression. These metabolic functions, once considered outside the purview of cytoskeletal proteins, highlight vimentin's evolving role as an integrator of structure and signaling in the tumor microenvironment (Table 1).

5. Therapeutic targeting of vimentin

Given its multifaceted role in tumor invasion, immune modulation, and metabolic adaptation, vimentin has emerged as a promising therapeutic target in cancer. Unlike structural cytoskeletal proteins that are ubiquitously expressed and indispensable in all cells, vimentin is often upregulated selectively in tumor and stromal cells undergoing epithelial-to-mesenchymal transition (EMT), inflammation, or stress. This differential expression makes it an attractive candidate for targeted therapies, imaging agents, and drug delivery systems(Ridge et al., 2022; Satelli et al., 2017).

5.1. Small molecule inhibitors

Several small molecules have been shown to modulate vimentin function or expression. Among the most studied is withaferin A (WFA), a steroidal lactone derived from *Withania somnifera (*Falkenberg et al., 2017*)*. WFA binds covalently to vimentin, disrupting filament assembly and inducing its proteasomal degradation. In preclinical models, WFA has demonstrated potent anti-tumor effects by impairing cancer cell migration, angiogenesis, and metastasis across breast, pancreatic, and ovarian cancers. Withaferin A has demonstrated anti-tumor effects in preclinical models of breast, pancreatic, and ovarian cancers (Bargagna-Mohan et al., 2007; Thaiparambil et al., 2011; Xing et al., 2023).

Other small molecules, such as simvastatin, have been shown to downregulate vimentin expression indirectly through modulation of the mevalonate pathway, which influences prenylation and actin-vimentin crosstalk (Trogden et al., 2018; Warita et al., 2014; Yin et al., 2018). Similarly, salinomycin, a compound known to target cancer stem cells, has been reported to reduce vimentin levels while reversing EMT phenotypes in carcinoma cells (Dewangan et al., 2017; X. Huang et al., 2016; Kusunoki et al., 2013).

Despite these promising findings, small-molecule inhibitors of vimentin have yet to reach clinical trials, in part due to concerns about off-target effects and the lack of vimentin-specific pharmacodynamic markers.

5.2. Monoclonal antibodies and imaging agents

Vimentin presence on the cell surface in tumor cells, endothelial cells, and immune cells has enabled the development of monoclonal antibodies and imaging tools. One such antibody, SC5, recognizes surface vimentin and has been used to visualize tumors via immunofluorescence and PET imaging (Arrindell and Desnues, 2023; Lalioti et al., 2022; Nakamura et al., 2022).

Additionally, nanobody-based probes and radiolabeled vimentin antibodies are being developed for non-invasive tumor imaging and as potential vehicles for drug delivery. For instance, radiolabeled anti-vimentin antibodies have been used to identify metastatic lesions in preclinical models, offering a new avenue for detecting invasive cancer

Table 1
Roles of Vimentin in Stromal Cells vs. Cancer Cells. Vimentin plays distinct and sometimes overlapping roles in stromal cells and cancer (tumor) cells within the tumor microenvironment (TME). In cancer cells, vimentin is central to EMT, invasion, immune evasion, metabolic flexibility, and the release of pro-invasive extracellular vesicles. In stromal cells, vimentin supports ECM remodeling (via CAFs), immune regulation (TAMs, MDSCs), angiogenesis (endothelial cells), and facilitates communication and support for tumor progression. This compartmental distinction is critical for understanding vimentin's multifaceted roles in cancer biology and for developing targeted therapies that address both tumor-intrinsic and stromal functions.

Function/Process	Tumor Cells	Stromal Cells	References
EMT & Cytoskeletal Remodeling	Drives EMT, increases motility, enables invasion	Supports matrix remodeling, provides structural support	Parvanian et al., (2025); Cheng et al., (2016); Usman et al., (2021); Virtakoivu et al., (2015); Battaglia et al., (2018); Karoii et al., (2022); Lamouille et al., (2014); Leduc and Etienne-Manneville, (2015); Youssef and Nieto, (2024); Ridge et al., (2022); Haerinck et al., (2023); Lavenus et al., (2020)
Focal Adhesion & ECM Interactions	Regulates integrin recycling, focal adhesion, traction force	CAFs remodel ECM, secrete fibronectin and tenascin C	Parvanian et al., (2025); Alisafaei et al., (2024); Shao et al., (2023); Zholudeva et al., (2024); Ho Thanh et al., (2024); Ostrowska-Podhorodecka et al., (2022); Anderson and Simon, (2020)
Extracellular Vesicles (EVs) & Invasion Cargo	EVs carry vimentin, MMPs, EMT factors to promote invasion	Stromal EVs help form metastatic niches, facilitate invasion	Parvanian et al., (2025); Adolf et al., (2019); Bucki et al., (2022); Fasipe et al., (2018); Martinez-Vargas et al., (2023); Shigyo et al., (2015); Suprewicz et al., (2021); van Beijnum et al., (2022); Booijink et al., (2024); Cheytan et al., (2025)
Surface Vimentin & Immune Evasion	Surface vimentin aids immune escape (e.g., modulates NK cells)	Expressed on immune/ endothelial cells, modulates immunity	Suprewicz et al., Parvanian et al., (2023a); Glassy, (2025); Liu et al., (2020); Garg et al., (2006); Suprewicz et al., (2021); Shigyo et al., (2015); Arrindell and Desnues, (2023); Starr et al., (2012); Nieminen et al., (2006); Bastounis et al., (2018); Gu et al., (2024); Yuan et al., (2025); Thalla et al., (2022)
Antigen Presentation & Phagocytosis	Alters antigen presentation, may mimic apoptotic cells	Required for APCs (DCs, macrophages) to process antigens	Suprewicz et al., (2024); Parvanian et al., (2023b); Pereira et al., (2005); Thiagarajan et al., (2013); Roghanian et al., (2010); Shaebani et al., (2022); Yu et al., (2018); Thalla et al., (2022); Alyaseer et al., (2020); Dos Santos et al., (2015)
Immune Cell Migration & Function	Indirectly regulates immune exclusion via signaling	Essential for immune cell motility, synapse formation, TAM/MDSC function	Nieminen et al., (2006); Parvanian et al., (2023b); Bai et al., (2024); Stankevicins et al., (2019); Billadeau et al., (2007); Li et al., (2015); Da et al., n.d.; Ma et al., (2024); Arrindell and Desnues, (2023)
Mitochondria Interactions	Controls mitochondrial positioning, supports OXPHOS, plasticity	Similar regulation in CAFs/ endothelial cells for TME support	Chernoivanenko et al., (2015); Matveeva et al., (2010); Nekrasova et al., (2011); Tang et al., (2008); Berr et al., (2023); Ding et al., (2021); Huynh et al., (2024); Mohanasundaram et al., (2022); Lavenus et al., (2020)
Glycolytic Reprogramming & Oxidative Stress	Organizes glycolytic enzymes, buffers oxidative stress	Facilitates antioxidant defense, metabolic adaptation	Komura et al., (2012); Rho et al., (2009); Yang et al., (2023); Matveeva et al., (2010); Prez-Sala et al., 2015; Biskou et al., (2019); Martnez-Cenalmor et al., 2024; Xiang et al., (2022)
Crosstalk with Hypoxia & HIF-1α	Upregulated by HIF-1α, reinforces hypoxia signaling, angiogenesis	Responds to hypoxia, influences angiogenesis and ECM	van Beijnum et al., (2022); Shamshiripour et al., (2024); Kidd et al., (2014); Li et al., (2017); Zhu et al., (2016); Wang et al., (2011); Lin et al., (2019); Lalioti et al., (2022); Arrindell and Desnues, (2023)
Therapeutic Targeting	Targeted to reduce invasion, immune evasion, metabolic adaptation	Targeted to disrupt stromal support, EV biogenesis, immune suppression	van Beijnum et al., (2022); Parvanian et al., (2023b); Arrindell and Desnues, (2023); Ridge et al., (2022); Bargagna-Mohan et al., (2007); Trogden et al., (2018); Dewangan et al., (2017); Lalioti et al., (2022); Zottel et al., (2023); Wu et al., (2021); Bravaccini et al., (2021); Chakraborty et al., (2019); Berr et al., (2023)

phenotypes. Radiolabeled anti-vimentin antibodies have enabled tumor visualization in preclinical models; translational studies are ongoing to assess clinical utility. (Gettemans and de Dobbelaer, 2021; Nunes Vicente et al., 2022; Tsuruta et al., 2023; van Beijnum et al., 2022; Zottel et al., 2023).

Therapeutic applications of these antibodies could include targeted delivery of cytotoxic agents or immune checkpoint inhibitors to vimentin-expressing cells in the tumor microenvironment. However, further validation in human models is needed to ensure specificity and safety.

5.3. *Vimentin-targeting nanoparticles and extracellular vesicles*

Given vimentin's involvement in extracellular vesicle (EV) biogenesis and cargo selection (Parvanian et al., 2020, 2021, 2023a, 2023b), innovative strategies now aim to exploit vimentin itself as a delivery or targeting platform. For example, polymeric nanoparticles modified with chitobionic acid have been developed to bind vimentin's lectin-like domain, enabling kidney-specific gene delivery in models of renal injury (Kim et al., 2014; Kumar et al., 2024; Mathew et al., 2021).

Furthermore, the vimentin-binding compound R491 has shown promise in inhibiting the release of cancer exosomes and metastasis. R491 functions by binding to vimentin and reducing exosome secretion through retention of intraluminal vesicles within cells. This approach has demonstrated efficacy in reducing migration and invasion in lung and pancreatic cancer cells, as well as decreasing exosome levels in mouse blood (Wu et al., 2021).

5.4. *Combination therapies*

Emerging evidence suggests that targeting vimentin in combination with other therapies may enhance treatment efficacy. For instance, combining vimentin inhibition with immune checkpoint blockade has shown synergistic effects in preclinical models. Vimentin knockout or inhibition can increase tumor immunogenicity and T cell infiltration, potentially overcoming resistance to immunotherapy. Synergistic effects of vimentin inhibition in combination with immune checkpoint blockade have been observed in animal models; however, clinical validation is still needed.

(Berr et al., 2023; Bravaccini et al., 2021; Chakraborty et al., 2019; van Beijnum et al., 2022; D. Zhang, Zhao, et al., 2024).

Additionally, vimentin-targeted therapies may sensitize cancer cells to conventional chemotherapies. For example, withaferin A treatment has been shown to enhance the efficacy of cisplatin in ovarian cancer models by disrupting vimentin-mediated chemoresistance mechanisms (Kakar et al., 2012; 2014; Noh et al., 2016).

Moreover, the therapeutic benefits of vimentin-targeting agents extend beyond oncology. For example, a recent study demonstrated that an oral vimentin inhibitor exhibited anti-inflammatory and host-directed antiviral activity in models of COVID-19, highlighting the broader immunoregulatory capacity of vimentin as a drug target (Z. Li et al., 2021).

As research in this field progresses, the development of combination strategies that leverage vimentin's multifaceted roles in tumor biology may offer new avenues for improving cancer treatment outcomes.

6. Challenges and future directions

While vimentin represents a compelling therapeutic target, several challenges remain. First, as a structural protein, complete inhibition of vimentin may result in undesired toxicity in wound-healing tissues or activated immune cells. Selective targeting strategies must distinguish tumor-specific forms of vimentin, such as those with post-translational modifications (PTMs) like phosphorylation or citrullination, which are enriched in cancer (Arrindell and Desnues, 2023; Parvanian et al., 2023b). Second, functional redundancy with other intermediate filaments and compensatory signaling may limit the efficacy of monotherapies targeting vimentin. Therefore, combining vimentin-targeting agents with other therapies such as immune checkpoint inhibitors**,** anti-angiogenics**,** or metabolic modulators may yield synergistic effects (van Beijnum et al., 2022). Lastly, there is a growing need for biomarkers to identify tumors that depend on vimentin for invasion and survival, as not all cancers exhibit high vimentin expression. Vimentin-positive circulating tumor cells have shown promise as biomarkers in pancreatic cancer, correlating with tumor burden and treatment response (Wei et al., 2019).

Additionally, hypermethylated TWIST1/Vimentin promoters in urine samples have demonstrated potential for non-invasive detection of bladder cancer (C. Zhang, Xu, et al., 2024). These findings highlight the potential of vimentin-based biomarkers to guide personalized therapy, though further validation is needed across different cancer types. However, it is important to note that preclinical outcomes with vimentin inhibition have been variable across cancer models. In some systems, vimentin knockout reduces metastasis, while in others it produces only modest effects, reflecting model-dependent compensatory pathways and tumor heterogeneity (Mendez et al., 2010; Cheng et al., 2022).

Despite advances, several knowledge gaps remain: the precise mechanisms by which vimentin's post-translational modifications control function in distinct TME compartments; the clinical relevance of vimentin-positive EVs as biomarkers; and the safety and specificity of vimentin-targeted therapies. Future studies should use spatial transcriptomics and conditional knockout models to dissect compartment-specific roles and develop selective inhibitors targeting tumor-specific vimentin modifications.

The evolving understanding of the role of vimentin in cancer biology continues to reveal surprising complexity and relevance far beyond its classical cytoskeletal functions. As new technologies and conceptual frameworks emerge, several key areas are shaping future research directions for vimentin in the tumor microenvironment TME.

Vimentin in Stromal vs. Tumor Compartments: While much attention has focused on vimentin expression in tumor cells undergoing EMT, increasing evidence suggests that stromal cells, particularly CAFs (Ho Thanh et al., 2024; Ostrowska-Podhorodecka et al., 2022), TAMs (Bai et al., 2024; Y. Zhang, Ding, et al., 2024), and endothelial cells (Arrindell and Desnues, 2023; Lalioti et al., 2022; Nakamura et al., 2022) also rely on vimentin for function and plasticity. Dissecting the respective contributions of tumor-intrinsic versus stromal vimentin remains particularly challenging in vivo, as both compartments can contribute to extracellular vimentin pools that influence immune modulation and metastasis. Conditional knockout models and spatial transcriptomics can help elucidate the unique contributions of vimentin in stromal versus epithelial compartments and how these interactions shape tumor progression. Distinct compartmental roles of vimentin, tumor cell-intrinsic versus stromal, shape the TME's invasive, immune, and metabolic landscape. Conditional knockout models and spatial transcriptomics will be essential to unravel these context-specific functions and their implications for therapy.

Post-Translational Modifications and Functional Plasticity: Vimentin is subject to a wide range of PTMs, including phosphorylation, glycosylation, citrullination, and oxidation, that dynamically regulate its assembly, interactions, and functions. These PTMs may serve as context-dependent switches that fine-tune vimentin's behavior during cellular stress, immune activation, or therapeutic intervention (Snider and Omary, 2014). Future studies leveraging mass spectrometry and single-cell proteomics could identify distinct vimentin "modiforms" as biomarkers or targets in specific cancer contexts.*Vimentin and Phase Separation:* A novel and speculative frontier in vimentin biology involves its potential role in biomolecular condensates and phase-separated domains. Phase separation, a process by which proteins and nucleic acids demix from the cytoplasm to form membraneless organelles has been implicated in transcriptional control, signal transduction, and stress responses. Vimentin intrinsically disordered regions (IDRs), along with its ability to rapidly assemble/disassemble and interact with other scaffolding proteins, raise the possibility that it may participate in or regulate phase-separated compartments, especially under stress or hypoxic conditions (Basu et al., 2025; Martínez-Cenalmor, Martínez, Moneo-Corcuera, Jiménez, et al., 2024; Pérez-Sala and Zorrilla, 2025). If validated, this property could further explain how vimentin coordinates the spatiotemporal organization of signaling complexes and metabolic enzymes in the TME. However, at present, these phase-separation functions remain speculative, supported primarily by in vitro or computational evidence rather than physiological validation.

Integration into Multimodal Therapeutics: As the field advances toward precision oncology, vimentin may serve not only as a target but also as a companion biomarker to inform therapy decisions. For instance, tumors with high vimentin expression or vimentin-positive EV signatures could be prioritized for anti-invasive therapies, immune checkpoint inhibitors, or metabolic modulators. Moreover, combining vimentin-targeting strategies with immunotherapies could enhance T cell infiltration and reverse immune suppression in vimentin-rich tumor niches. Vimentin-based imaging agents could also support non-invasive tumor phenotyping and real-time monitoring of EMT status or metastatic risk.

7. Conclusion

Vimentin has evolved from being viewed as a mere cytoskeletal scaffold and EMT marker to a central regulator of tumor progression, orchestrating processes such as invasion, immune modulation, and metabolic adaptation within the TME. Through its roles in cytoskeletal dynamics, extracellular vesicle biology, antigen presentation, and redox homeostasis, vimentin enables cancer and stromal cells to adapt to hostile conditions and drive malignancy.

Importantly, selective upregulation of vimentin in tumors, its presence on the cell surface and within EVs, and its functional plasticity make it a promising therapeutic target and biomarker. A range of strategies, including small molecule inhibitors, monoclonal antibodies, and nanocarriers, are being developed to modulate its activity. Future directions should prioritize understanding vimentin's post-translational modifications, context-dependent functions, and interactions within phase-separated compartments, to fully harness its potential in precision oncology.

Ultimately, targeting vimentin offers a multifaceted approach to disrupt key cancer hallmarks and improve outcomes in aggressive tumors. Unlocking its biology could pave the way for innovative therapies that integrate structural targeting with immunometabolic reprogramming, reshaping the landscape of cancer treatment.

CRediT authorship contribution statement

Sepideh Parvanian: Writing – review & editing, Writing – original draft, Project administration, Funding acquisition, Conceptualization. **John E. Eriksson:** Writing – review & editing, Validation, Supervision, Resources, Project administration, Investigation, Funding acquisition, Conceptualization.

Declaration of Competing Interest

The authors declare no competing interests.

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Data availability

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

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