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REVIEW

SUBJECT COLLECTION: HOST–PATHOGEN INTERACTIONS

The diverse actions of cytoskeletal vimentin in bacterial infection and host defense

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ABSTRACT

Bacterial infection is a major threat to human health, with infections resulting in considerable mortality, urging the need for a more profound understanding of bacteria–host interactions. During infection of cells, host cytoskeletal networks constantly interact with bacteria and are integral to their uptake. Vimentin, an intermediate filament protein, is one such cytoskeletal component that interacts with bacteria during infection. Although vimentin is predominantly present in the cytoplasm, it also appears in a secreted form or at the surface of multiple cell types, including epithelial cells, endothelial cells, macrophages and fibroblasts. As a cytoplasmic protein, vimentin participates in bacterial transportation and the consequential immune-inflammatory responses. When expressed on the cell surface, vimentin can be both pro- and anti-bacterial, favoring bacterial invasion in some contexts, but also limiting bacterial survival in others. Vimentin is also secreted and located extracellularly, where it is primarily involved in bacterial-induced inflammation regulation. Reciprocally, bacteria can also manipulate the fate of vimentin in host cells. Given that vimentin is not only involved in bacterial infection, but also the associated life-threatening inflammation, the use of vimentin-targeted drugs might offer a synergistic advantage. In this Review, we recapitulate the abundant evidence on vimentin and its dynamic changes in bacterial infection and speculate on its potential as an anti-bacterial therapeutic target.

KEY WORDS: Vimentin, Intermediate filaments, Bacterial infection, Bacterial invasion, Bacterial transportation, Immune-inflammatory responses

Introduction

During infection, the interaction between bacteria and host determines the ability of the bacteria to survive and spread (Sukumaran et al., 2021; Yang et al., 2015). Upon invading, bacteria hijack host cells as an environment for survival and transmission, and host cell immune signals are activated for antimicrobial responses (Chisholm et al., 2006; Hooper et al., 2012; Pinaud et al., 2018).

Bacteria–host interactions during invasion include utilization of the host cytoskeleton, of which intermediate filaments (IFs) are an essential component (Mak and Brüggemann, 2016). Compared with other cytoskeletal components, such as actin and microtubules, IFs show a unique combination of flexibility, extensibility and toughness that afford mechanical resilience to the cell (Hu et al., 2019; Patteson et al., 2020a; van Bodegraven and Etienne-Manneville, 2021). These mechanical characteristics protect the cell against damage in various conditions, such as nuclear damage during cell migration (Patteson et al., 2019), shear stress (Flitney et al., 2009; Helmke et al., 2000) and importantly, pathogen infections (Geisler and Leube, 2016).

Vimentin, a type III IF protein, is mainly expressed in mesenchymal cells derived from mesoderm, such as fibroblasts, endothelial cells, neutrophils and macrophages, which interact widely with pathogens (Fuchs and Weber, 1994; Kidd et al., 2014; Mor-Vaknin et al., 2003). Vimentin IFs are formed through polymerization of a single protein, unlike other IFs, such as keratin IFs or neurofilaments, which are copolymers of multiple distinct but related gene products (Herrmann and Aebi, 2016). Vimentin monomers consists of a non-helical amino (N)-terminal head, a conserved central α-helical rod and a carboxy (C)-terminal tail domain. During polymerization, the rod domains first promote the parallel association of monomers into dimers, then dimers bind in an antiparallel manner to form soluble apolar tetramers, considered the structural units for vimentin polymerization. Further lateral assembly of eight tetramers to form unit length filaments (ULFs) is followed by longitudinal annealing and radial compaction to generate insoluble mature vimentin filaments (Herrmann and Aebi, 2016; Zhang et al., 2021).

In recent decades, vimentin has been shown to play both mechanical and non-mechanical roles in the cell through its dynamic changes regulated by post-translational modifications and intracellular proteases (Lowery et al., 2015; Patteson et al., 2020b). Its mechanical functions mainly involve the maintenance of cell morphology, cell adhesion and migration, cell elasticity and subcellular localization of organelles. Meanwhile, its non-mechanical functions are becoming more appreciated, including signaling roles in wound healing and lipogenesis, marking circulating tumor cells and mediating the infection of pathogens (Ivaska et al., 2007; Liu et al., 2019; Mitra et al., 2015; Patteson et al., 2020b; Snider and Omary, 2014; van Engeland et al., 2019). In addition to its function as a cytosolic protein, studies have also revealed the existence of cell surface vimentin (CSV) and secreted vimentin, which are involved in cell activation and inflammatory responses (Adolf et al., 2019; Chi et al., 2012; Ghosh et al., 2018; Lam et al., 2018; Mor-Vaknin et al., 2003).

This Review summarizes the diverse interactions between vimentin and bacteria, highlighting the functional and dynamic changes vimentin undergoes during bacterial infection. We discuss how vimentin participates in the bacterial infection life cycle, focusing mainly on entry and trafficking, as well as the host defense response to invoke inflammation and pathogen clearance.

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Furthermore, we illustrate how bacterial infection changes the fate of vimentin to further manipulate host cellular processes, including epithelial–mesenchymal transition (EMT), cell differentiation and abnormal inflammatory responses.

Cytoplasmic vimentin and bacterial infection

As an important component of the cytoskeleton, vimentin forms a unique filamentous network in the cytoplasm. During bacterial infection, cytoplasmic vimentin regulates bacterial transport and mediates inflammatory signal transduction (Gasse et al., 2009). We summarize the interactions between cytoplasmic vimentin and bacteria and the involved virulence factors (Table 1).

Cytoplasmic vimentin in bacterial transportation

During invasion, bacteria typically hijack the host cytoskeleton for further trafficking. To escape detection from immune signals and/or degradation by lysosomes, many bacteria are transported in a form of vacuole called bacteria-containing vacuoles (BCVs) (Creasey and Isberg, 2014), and cytoplasmic vimentin was found mainly to regulate bacterial transportation and replication via BCVs. For example, *Salmonella enterica* serovar Typhimurium (*S.* Typhimurium) is a facultative intracellular pathogen that causes gastroenteritis in susceptible humans and fatal typhoid-like affliction in mice (Tsolis et al., 2000). After invading the host cell, these bacteria enter a vacuole, named the *Salmonella*-containing vacuole (SCV). The bacteria begin to replicate when the SCV reaches the juxtanuclear area. It has been shown that vimentin networks aggregate around SCVs from 7 h post-infection onwards (Guignot and Servin, 2008) (Fig. 1). Importantly, when vimentin is knocked down, SCVs become scattered throughout the cytoplasm, indicating that vimentin is critical in maintaining SCVs in the juxtanuclear area (Guignot and Servin, 2008). These results are consistent with the common role of vimentin in controlling the structure and localization of subcellular organelles (Toivola et al., 2005). The *S.* Typhimurium effector protein SptP also interacts with cytoplasmic vimentin, inducing recruitment of vimentin to the *Salmonella*-induced membrane ruffles (Murli et al., 2001). Vimentin is also key in *Chlamydia trachomatis* replication within BCVs. *C. trachomatis* vacuoles are stabilized by a scaffolding network made of F-actin and vimentin filaments, which encapsulate the vacuoles (Kumar and Valdivia, 2008) (Fig. 1). The protease *Chlamydia* protease-like activity factor (CPAF), secreted by *C. trachomatis*, targets and cleaves the head domain of vimentin and alters its properties, thus regulating the toughness and flexibility of vacuoles (Kumar and Valdivia, 2008; Snider et al., 2018; Tarbet et al., 2018). Another bacterium that utilizes vacuoles for replication is *Anaplasma phagocytophilum*, which causes human granulocytic anaplasmosis disease, one of the most common tick-borne diseases (Stuen et al., 2013). This unusual obligate intracellular pathogen selectively adheres to polymorphonuclear leukocytes, the most abundant innate immune cells in the circulation and one of the most important lines of defense in innate immunity (Nicu and Loos, 2016; Yago et al., 2003). In infected cells, *A. phagocytophilum* resides and duplicates within *A. phagocytophilum*-occupied vacuoles (ApVs). Studies have shown that both vimentin and keratin IF proteins aggregate to surround ApVs. In addition, polySUMOylation, the attachment of small ubiquitin-like modifier (SUMO) chains (Yang and Zhang, 2014), increases the solubility of vimentin, which contributes to its rearrangement around ApVs (Fig. 1). Consistent with this, more vimentin exists in an insoluble state in *A. phagocytophilum*-infected cells than in uninfected cells. The bacterial load is significantly reduced when cytoplasmic vimentin is inhibited by Withaferin A (WFA), which binds to soluble vimentin and causes its aggregation (Bargagna-Mohan et al., 2007). Therefore, *A. phagocytophilum* modulate vimentin to construct their vacuolar niche and promote optimal survival (Truchan et al., 2016). In addition, vimentin surrounding ApVs interacts with *A. phagocytotopulum* toxin A protein (AptA) to activate the mammalian ERK1 and ERK2 (also known as MAPK3 and MAPK1, respectively) mitogen-activated protein kinase (MAPK), which is essential for *A. phagocytophilum* survival (Sukumaran et al., 2011; Xiong et al., 2009; Xiong and Rikihisa, 2011). Thus,

Table 1. Summary of the interactions between bacteria and the distinct forms of vimentin

Bacteria	Virulence factors	Proposed or established role	Host cells	References
Cytoplasmic vimentin				
S. Typhimurium	SptP and SopB	Pro-bacterial	Epithelial cells	Fu and Galán, 1998; Tahoun et al., 2012
C. trachomatis	CPAF	Pro-bacterial	HeLa cells	Kumar and Valdivia, 2008
A. phagocytophilum	AptA	Pro-bacterial	Leukocytes	Sukumaran et al., 2011; Truchan et al., 2016
–	LPS	–	Macrophages	Dos Santos et al., 2015
M. tuberculosis	ESAT-6	–	Macrophages	Mishra et al., 2010; Mahesh et al., 2016
Helicobacter pylori	CagA	Pro-bacterial	Gastric cells	Yu et al., 2014; Wroblewski et al., 2015
Streptococcus pyogenes	SpyA	–	Macrophage	Icenogle et al., 2012
P. aeruginosa	ExoA and ExoS	–	Kidney cells	Sharpe et al., 1980; Coburn et al., 1989; Kroken et al., 2022
Cell surface vimentin				
E. coli K1	IbeA	Pro-bacterial	BMVEs	Zou et al., 2006; Chi et al., 2010, 2012
Group B *Streptococcus*	BspC	Pro-bacterial	BMVEs	Deng et al., 2019; Beninati et al., 2019
L. monocytogenes	InlF	Pro-bacterial	BMVEs	Ghosh et al., 2018
P. acnes	–	Pro-bacterial	Prostate cells	Mak et al., 2012
M. avium subspecies *hominissuis*	MBP-1	Pro-bacterial	Human respiratory epithelial cells	Babrak et al., 2015
S. flexneri	IpaC	Pro-bacterial	Mouse embryonic fibroblasts	Russo et al., 2016
E. coli	–	Pro-bacterial	HEK293 cells	Stevens et al., 2013
Extracellular vimentin				
C. botulinum	C3bot	–	Neurons	Adolf et al., 2019
–	LPS	–	Dendritic cells	Yu et al., 2018
E. coli	–	Anti-bacterial	Macrophages	Mor-Vaknin et al., 2003

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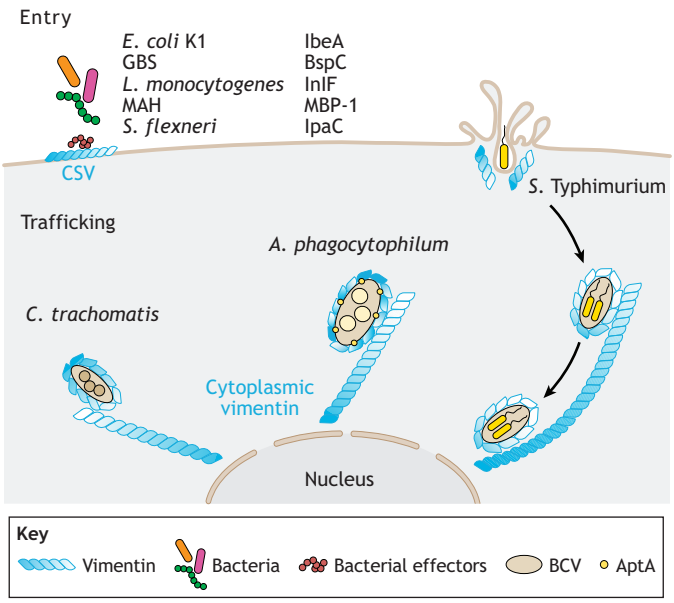

Fig. 1. Schematic illustration of how vimentin mediates bacterial entry and trafficking. CSV interacts with bacterial effectors to mediate bacterial entry. Highlighted are factors that mediate bacterial entry. Factors that mediates entry into brain BMECs are IbeA (*E. coli* K1 entry), BspC (GBS entry) and InlF (*L. monocytogenes* entry). CSV also interacts with MBP-1 during MAH entry into human respiratory epithelial cells, and the primary effector IpaC acts to promote the stable docking between *S. flexneri* and mouse embryonic fibroblasts. Cytoplasmic vimentin mediates bacterial trafficking. The *S.* Typhimurium effector protein SptP recruits cytoplasmic vimentin to *Salmonella*-induced ruffles, and cytoplasmic vimentin mediates the trafficking of SCVs to the juxtanuclear area. *C. trachomatis*-containing vacuoles are stabilized by vimentin scaffolds; here, cytoplasmic vimentin rearranges around the ApV, and the *A. phagocytotopulum* effector AptA interacts with vimentin to promote optimal bacterial survival in the vacuole niche.

cytoplasmic vimentin is involved in both the mechanical regulation of BCVs, as well as cell signaling events during bacterial infection. For a summary of these interactions, see Table 1.

Role of cytoplasmic vimentin in inflammation and immune responses upon bacterial infection

Vimentin displays a wide range of non-mechanical functions in the process of apoptosis and inflammation (Su et al., 2019a; Su et al., 2019b). In inflammatory and autoimmune diseases (Mortensen et al., 2015), vimentin can serve as a scaffold to coordinate immune defenses. This includes the localization of a number of pattern recognition receptors (PRRs), which mediate initial sensing of infection and the subsequent activation of the inflammatory response (Dos Santos et al., 2015; Mizushima and Levine, 2020; Thiagarajan et al., 2013) (Fig. 2), as well as autophagy, an important line of defense against pathogens in eukaryotes (Kroemer et al., 2010; Mizushima and Levine, 2020). Vimentin regulates autophagy by altering the re-localization of autophagosomes from the cytoplasm to the juxtanuclear region, given that treatment with the vimentin inhibitor WFA inhibits the fusion of autophagosomes and lysosomes, thus preventing their maturation autolysosomes (Biskou et al., 2019).

Acute lung injury (ALI) is associated with activation of the NOD-like receptor protein 3 (NLRP3) inflammasome and subsequent maturation of interleukin (IL)-1β, which leads to excessive inflammation (Gasse et al., 2009). It has been reported that vimentin colocalizes with NLRP3 and active caspase-1 during the onset of ALI (Gasse et al., 2009). In addition, the absence of vimentin suppresses the pathophysiological events of ALI in mice, including IL-1β expression, endothelial and alveolar epithelial barrier permeability and fibrosis, which are induced by lipopolysaccharides (LPS), bleomycin and asbestos, respectively (Dos Santos et al., 2015; Zhou et al., 2020). In contrast, vimentin knockdown in lung fibroblasts results in increased apoptosis and inflammatory cytokines, including tumor necrosis factor (TNF; also known as TNF-α), IL-1β, IL-6 and IL-10, when challenged with LPS (Pan et al., 2021). Whether this result differs due to cell-specific effects is worth further inquiry.

When challenged by LPS, caspase-3 is significantly upregulated in vimentin-deficient Jurkat T cells and reciprocally downregulated in vimentin-overexpressing cells (Su et al., 2019a). Levels of the cytokines IL-2, IL-10 and interferon γ (IFN-γ) are significantly lower in vimentin-deficient cells, whereas they are unchanged in vimentin-overexpressing cells (Su et al., 2019a), perhaps because the endogenous vimentin levels are already enough to help induce high levels of these cytokines when challenged by LPS. Moreover, vimentin depletion significantly enhances the metabolic and suppressive activity of regulatory T cells (Tregs) (McDonald-Hyman et al., 2018), although this was in the context of graft-versus-host disease, and not bacterial infection.

In addition to macrophage activation, differentiation and phagocytosis, vimentin is also involved in reactive oxygen species (ROS) production (Beneš et al., 2006; Mor-Vaknin et al., 2003). *Mycobacterium tuberculosis* (Mtb) is a highly adaptive pathogen that evolved with humans (Brites and Gagneux, 2015). Treating Mtb-infected macrophages with hydrogen peroxide (H_2O_2), a type of ROS, increases vimentin expression (Mahesh et al., 2016). In contrast, vimentin expression decreases in Mtb-infected macrophages treated with N-acetyl L-cysteine (NAC), a scavenger of ROS, suggesting vimentin expression is ROS dependent (Mahesh et al., 2016). Moreover, ectopic expression of the Mtb protein early secreted antigenic target of 6 kDa (ESAT-6) decreases both the level of ROS and the expression of vimentin in macrophages, which implies that Mtb-mediated downregulation of vimentin is, at least in part, due to the downregulation of ROS by the pathogen (Mahesh et al., 2016; Mishra et al., 2010). Interestingly, although ESAT-6 reduces vimentin expression, both ESAT-6 and vimentin are involved in the assembly of the NLRP3 inflammasome (Dos Santos et al., 2015), which is worthy of more investigation. In addition, ROS are involved in nuclear factor (NF)-κB activation and pro-inflammatory responses induced by LPS (Gloire et al., 2006). Interestingly, the incubation of macrophages with anti-vimentin antibodies increases the production of ROS (Mahesh et al., 2016). Additionally, vimentin-deficient phagocytes or vimentin-knockout mice challenged with *Escherichia coli* in the abdominal cavity produce more ROS and nitric oxide (NO) to kill bacteria (Mor-Vaknin et al., 2013). Together, these findings demonstrate that vimentin is a key metabolic and functional regulator of inflammatory responses, particularly involving ROS (Fig. 2), and provide evidence that regulation of vimentin might be used to treat bacterial infections.

CSV and bacterial infection

Although originally identified as a cytoplasmic protein (Steinert and Liem, 1990), vimentin has since been shown to also localize to the cell surface (Dupont et al., 2004; Segawa et al., 2005). Previous studies indicate that CSV mediates the landing of bacteria at specific membrane sites, where it acts as a receptor and/or coreceptor.

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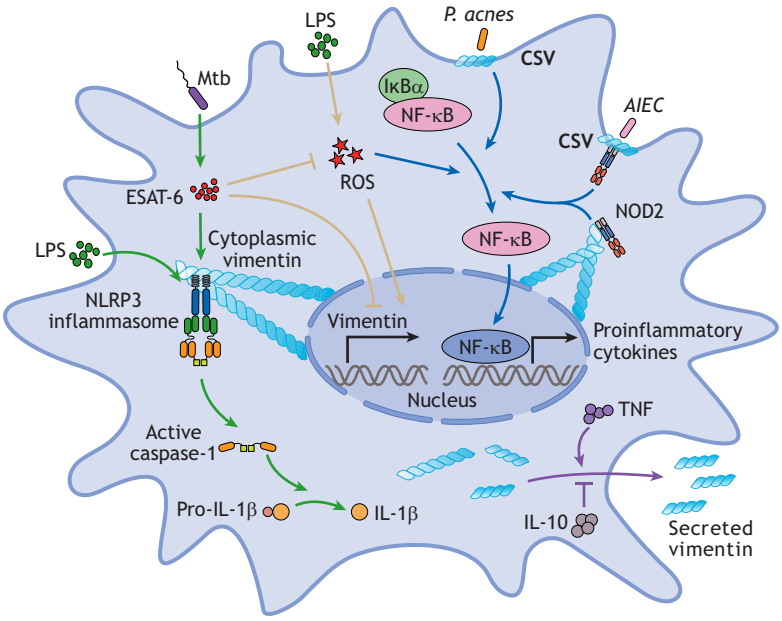

Fig. 2. Schematic illustration of vimentin functions during bacteria-induced inflammatory responses. CSV is crucial for the invasion of *P. acnes* and *AIEC* by inducing an NF-κB- and NOD2-mediated inflammatory response in macrophages (blue arrows). Cytoplasmic vimentin filaments serve as scaffolds for NLRP3 inflammasomes and NOD2. Upon LPS exposure, NLRP3 inflammasomes interact with and are activated by cytoplasmic vimentin, with subsequent maturation of IL-1β (green arrows). Additionally, ROS elevation promotes vimentin expression, as well as activation of NF-κB signaling. However, infection with Mtb results in a reduction in the level of vimentin and ROS via ESAT-6; this subsequently suppresses the activation of NLPR3 and NF-κB, accompanied by lower levels of pro-inflammatory cytokines (yellow arrows). Finally, secretion of vimentin is triggered by the pro-inflammatory cytokine TNF and blocked by the anti-inflammatory cytokine IL-10 (purple arrows).

Moreover, CSV has been found to participate in limiting bacterial survival (Stevens et al., 2013). In this section, we describe how CSV can both enhance bacterial infection and limit bacterial survival.

Involvement of CSV in bacterial entry

Meningitis, the inflammation of the meninges with high morbidity and mortality rates (Putz et al., 2013), is the most common serious infection in newborns (van der Flier, 2021). The pathogenic bacteria of meningitis include *E. coli* K1, group B *Streptococcus* (GBS) and *Listeria monocytogenes*, among others (Kim et al., 2009). The blood–brain barrier (BBB) is an important structure protecting against the invasion of pathogens into the brain and preventing meningitis (Huang et al., 2000; Kim, 2003). The BBB is formed by brain microvascular endothelial cells (BMECs), which have high endogenous vimentin expression (Zou et al., 2006). It has been reported that the interaction between IbeA, an *E coli* K1 effector, with the head domain of CSV is critical for *E coli* K1 invasion (Chi et al., 2010; Zou et al., 2006). In addition, IbeA and IbeA+ *E coli* K1 are able to induce clustering of vimentin at the surface of BMECs, which is required for the invasion process (Chi et al., 2010). GBS infection, the leading cause of meningitis, continues to increase in incidence and affects a wider age group with more diverse clinical manifestations, including skin, soft tissue, heart valve and urinary tract infections (Raabe and Shane, 2019). CSV interacts with BspC, the GBS surface factor, via its tail domain to promote bacterial adhesion to BMECs (Beninati et al., 2019; Deng et al., 2019). *L. monocytogenes* also utilize CSV as an invasion receptor to interact with the virulence factor InIF and promote bacterial invasion (Ghosh et al., 2018). In a mouse model deficient in vimentin, *L. monocytogenes* colonization in the brain is severely compromised (Ghosh et al., 2018). Another study found that extracellular matrix stiffness can regulate the susceptibility of mammalian host cells to *L. monocytogenes* infection and that this regulation depends on the level of CSV, which acted as host cell surface receptors (Bastounis et al., 2018).

In addition to meningitis-related pathogens, CSV is also critical for the invasion of other bacteria. *Propionibacterium acnes* was initially identified as being an important member of the skin microbiome and associated with acne vulgaris (Byrd et al., 2018). However, there is evidence suggesting it is related to other chronic diseases, such as prostate inflammation, including upregulation of inflammatory cytokines and chemokines (Perry and Lambert, 2011). *P. acnes* can effectively penetrate prostate cells expressing CSV. Antibody-mediated neutralization of CSV unveils the role of vimentin as a cell surface mediator for invasion of *P. acnes* (Mak et al., 2012).

CSV is also important for invasion of the *Mycobacterium avium* subspecies *hominissuis* (MAH), which causes respiratory diseases in immunocompromised patients, such as cystic fibrosis and chronic respiratory diseases (Daley, 2017). During initial airway colonization, MAH forms microaggregates consisting of three to 20 bacterial species on human respiratory epithelial cells via microaggregate-binding protein 1 (MBP-1; also known as general stress protein CsbD, encoded by MAV_3013), which leads to effective invasion towards mucous membranes (Babrak et al., 2015). Interestingly, vimentin interacts with MBP-1, and anti-vimentin antibody V9 blocks the binding of microaggregates to host cells (Babrak et al., 2015). *Shigella flexneri* employs the type III secretion system (T3SS) to inject effector proteins into target host cells, enabling bacterial infection (Puhar and Sansonetti, 2014; Ramos-Morales, 2012; Zhou and Galán, 2001). Invasion plasmid antigen C (IpaC), secreted via the T3SS, has been identified as the primary effector protein for epithelial cell invasion (Duncan-Lowey et al., 2020). CSV has been shown to interact with IpaC, which is required for the stable docking of *S. flexneri* to host cells and further triggers effector secretion (Russo et al., 2016). Together, the above studies conclude that bacteria invade host cells through interactions between key virulence factors and specific domains of CSV. Identifying the exact interaction sites requires further exploration before their interruption might be used as a potential target for therapy.

Role of CSV in bacterial clearance by mediating inflammatory responses

The initial sensing of a pathogenic infection is mediated by innate PRRs, which recognize and bind to pathogen-associated molecular patterns (PAMPs) to trigger the activation of inflammatory and antimicrobial signals (Takeuchi and Akira, 2010). Nucleotide binding oligomerization domain-containing protein 2 (NOD2), as

an intracellular PRR, binds to the ligand muramyl dipeptide (MDP) to induce pathogen transmission and clearance (Caruso et al., 2014). NOD2 mutations remain the strongest single genetic determinant of Crohn's disease (CD). Three disease-associated polymorphisms of NOD2, including R702W, G908R and L1007fs, all alter the leucine-rich repeat domain (LRR) of NOD2 (Packwood et al., 2010). Interestingly, NOD2 interacts with CSV through its LRR domain, and this interaction affects NOD2 localization on the cell membrane (Stevens et al., 2013). Moreover, NOD2 and CSV regulate the invasiveness and survival of adherent-invasive *E. coli* (*AIEC*) (Stevens et al., 2013). The vimentin inhibitor WFA effectively impairs the ability of NOD2 to limit bacterial survival by inhibiting NOD2-dependent NF-κB activation and autophagy (Stevens et al., 2013). These studies suggest that vimentin favors limiting bacterial survival by cooperating with NOD2 to mediate the inflammation responses. Moreover, vimentin expressed on the surface of apoptotic neutrophils can be used as an 'eat me' signal that is recognized by phagocytes (Moisan and Girard, 2006). It is worth mentioning that, although vimentin limits bacterial survival using the above mechanisms, depletion of vimentin or inhibition by WFA can also reduce bacterial invasion (Henderson and Stevens, 2012; Henderson et al., 2012; Stevens et al., 2013). Several studies support a pro-infection role of vimentin, but only few reports describe the role of vimentin in restricting bacterial infection. Therefore, the precise and complex antagonistic relationship between bacteria and cellular vimentin deserves further investigation.

Secreted vimentin and bacterial infection

Secreted vimentin and immune cells

Macrophages can secrete vimentin and this process is regulated by inflammatory factors (Mor-Vaknin et al., 2003); the anti-inflammatory cytokine IL-10 blocks vimentin secretion, whereas the pro-inflammatory cytokine TNF triggers vimentin secretion (Mor-Vaknin et al., 2003). During bacterial infection, secreted vimentin promotes innate inflammatory responses by increasing the bactericidal capacity of macrophages and the level of active oxidative metabolite production (Mor-Vaknin et al., 2003). The *Clostridium botulinum* C3 exoenzyme (C3bot) is a bacterial ADP-ribosomal transferase that inhibits Rho family small GTPases. It has been used as a pharmacological tool to investigate cellular Rho function and to repair neuronal injury (Loske et al., 2012). Astrocytes have been shown to secrete exosomes containing vimentin, which facilitates C3bot interactions with neurons and neuronal recovery after injury (Adolf et al., 2019). Another study has shown that secreted vimentin promotes LPS-induced activation of human dendritic cells by regulating the secretion of IL-6, IL-12 and IL-10 (Fig. 2). Among them, the anti-inflammatory cytokine IL-10 prevents the differentiation of T cells to Th1 cells, thereby reducing the development of tissue damage caused by autoimmunity (Yu et al., 2018). The interactions between secreted vimentin, bacteria and the virulence factors are summarized in Table 1.

Neutrophils, the most abundant type of leukocyte (white blood cell) in the body, protect the body from harmful microbial infections, especially those caused by bacterial and fungal pathogens (van Rees et al., 2016). Neutrophils tend to adhere to endothelial cells via P-selectin, an early step in acute inflammatory responses (Liou et al., 2013). However, excessive activation of leukocytes causes autoimmune diseases, including ALI (Lam et al., 2018). Platelets can repair damage and maintain vascular integrity through adhesion, that is, platelet–platelet interaction (Berger et al., 1998). Recombinant vimentin has been shown to decrease the adhesion of neutrophils to the platelet receptor P-selectin, thereby reducing ALI (Lam et al., 2018). It has been speculated that secreted vimentin has the same ability. Whether secreted vimentin behaves similarly to recombinant vimentin is unknown. Several studies have reported the presence of circulating vimentin in peripheral blood (Bay-Jensen et al., 2013; Li et al., 2017). Therefore, whether naturally occurring circulating vimentin also participates in immune function through P-selectin, and thus regulation of leukocyte–platelet interactions, deserves further investigation.

Post-translational regulation of secreted vimentin by citrullination

Citrullination, the conversion of the amino acid arginine to citrulline, is catalyzed by peptidyl arginine deiminases (PADs) (Vossenaar et al., 2004). Neutrophil extracellular traps (NETs), released via a form of cell death called NETosis, consist of a chromatin meshwork decorated with antimicrobial peptides typically present in neutrophil granules (Brinkmann et al., 2004). NETs bind microorganisms, degrade virulence factors and kill bacteria (Brinkmann et al., 2004; Hirschfeld et al., 2017; Mutua and Gershwin, 2021). During NETosis, citrullinated vimentin is externalized into NETs (Khandpur et al., 2013). Interestingly, rheumatoid arthritis (RA) is characterized by the breakdown of self-tolerance to citrulline antigens, producing autoantibodies to citrullinated protein antigens (ACPAs) (Corsiero et al., 2016; Klareskog et al., 2014). Citrullinated vimentin is one of the candidate antigens (Corsiero et al., 2016; Luime et al., 2010; Van Steendam et al., 2011). Notably, RA serum and immunoglobulin fractions significantly enhance NETosis in RA patients with high ACPA levels (Khandpur et al., 2013). Neutrophils externalize citrullinated autoantigens associated with RA pathogenesis, and anti-citrullinated vimentin antibodies can effectively induce NET formation (Khandpur et al., 2013). In addition, NETs significantly enhance the inflammatory response in RA and osteoarthritis synovial fibroblasts, including the induction of IL-6, IL-8, chemokines and adhesion molecules (Khandpur et al., 2013). These observations suggest that enhanced NETosis, with externalized citrullinated vimentin, promotes abnormal adaptive and innate immune responses in joints and the periphery during RA pathogenesis and perpetuates the pathogenic mechanisms of the disease (Khandpur et al., 2013).

Bacterial infection regulates the fate of vimentin in host cells

In addition to participating in bacterial infection, vimentin in host cells can also be adversely affected by various bacteria (Table 1). Vimentin is often used as a marker of mesenchymal-derived cells, or cells undergoing EMT during normal development and metastatic progression (Satelli and Li, 2011). *S.* Typhimurium specifically targets microfold cells (M cells), which in contrast to other intestinal cells, express vimentin (Kraehenbuhl and Neutra, 2000; Tahoun et al., 2011). The T3SS effector protein SopB of *S.* Typhimurium increases the expression levels of host cell vimentin, which induces the transformation of follicular-associated epithelium (FAE) into M cells (Tahoun et al., 2012). This promotes bacterial infection by activating the Wnt/β-catenin and NF-κB signaling pathways (Tahoun et al., 2012). This is also exemplified by *H. pylori*, a bacterium found on epithelial cells in the gastric mucosa (Huang et al., 2017). Studies have shown that vimentin expression increases in *H. pylori*-infected cells, inducing EMT-like phenotypic changes in gastric cancer, which contribute to gastric carcinogenesis (Fig. 3) (Bessède et al., 2014; Lamouille et al., 2014; Marques et al., 2018; Wroblewski et al., 2015; Yu et al., 2014). A recent study has shown that intracellular bacteria in breast tumor cells promote tumor

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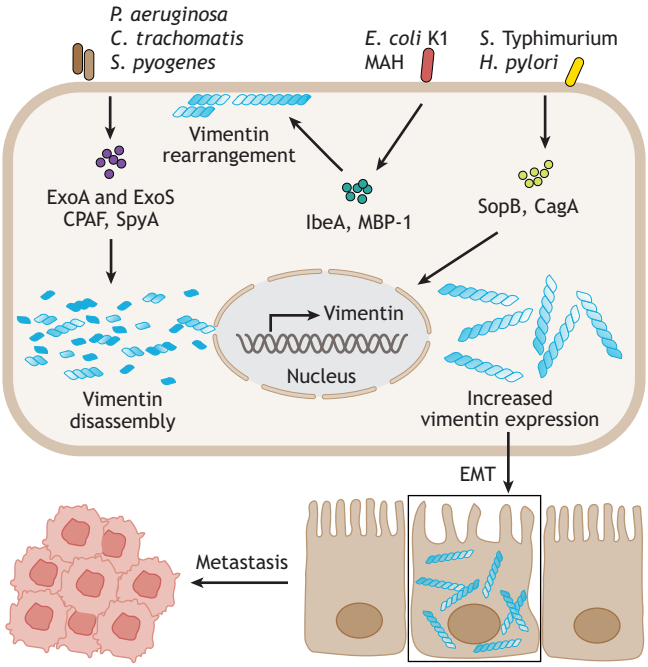

Fig. 3. Schematic illustration of bacteria-mediated regulation of vimentin after infection. Overview of bacterial factors that regulate vimentin rearrangements. The *E. coli* K1 effector IbeA induces vimentin clustering in BMECs, and the MAH effector MBP-1 induces vimentin aggregation in human respiratory epithelial cells. Other bacteria induce vimentin disassembly; the *P. aeruginosa* effector ExoA destroys the filamentous structure of vimentin and its effector ExoS disassembles vimentin by catalyzing ADP ribosylation. Furthermore, the protease CPAF, secreted by *C. trachomatis*, cleaves the head domain of vimentin and alters its cytoskeletal properties. Finally, SpyA is an ADP ribotransferase secreted by *S. pyogenes* that modifies the arginine head domain of vimentin, causing its tetramer subunit to collapse. Some bacteria promote vimentin expression to induce host cell EMT. For example, the effector protein SopB of *S.* Typhimurium induces a transition from follicular-associated epithelium into M cells, which are marked by vimentin, whereas *H. pylori* CagA induces EMT-associated changes in gastric cancer, including elevated vimentin expression, which results in increased hematogenous metastasis of tumors.

metastasis by reducing the density of actin stress fibers (Fu et al., 2022). Notably, vimentin is a marker of EMT, and numerous studies have shown that its expression increases during bacterial infection-induced carcinogenesis as well as increasing hematogenous metastasis of tumors (Abd-El-Raouf et al., 2020; Chen et al., 2020; Choi et al., 2015; Hofman and Vouret-Craviari, 2012). Whether vimentin is involved in intracellular bacteria-induced tumor metastasis deserves further attention.

Several bacterial factors are reported to interfere with vimentin to regulate its assembly and disassembly through post-translational modifications (Icenogle et al., 2012). SpyA is a streptococcal ADP ribosyltransferase that modifies the arginine head domain of vimentin (including arginine residues 44, 49 and 63), to cause the collapse of the tetramer subunit of vimentin (Fig. 3) (Coye and Collins, 2004; Icenogle et al., 2012; Snider and Omary, 2014). SpyA also triggers caspase-1-dependent inflammatory response and reduces filamentous vimentin in macrophages (Icenogle et al., 2012; Lin et al., 2015). In addition, the effector protein Exotoxin S (ExoS) of *Pseudomonas aeruginosa* can catalyze ADP-ribosylation and disassemble vimentin (Coburn et al., 1989; Kroken et al., 2022). Exotoxin A (ExoA) of *P. aeruginosa* has been shown to disrupt the filamentous structure of vimentin, while causing no discernible effect on microtubules or microfilaments (Sharpe et al., 1980).

As a dynamic structure, vimentin can be regulated by cell cycle-dependent endogenous phosphorylation, which usually occurs on its N-terminal head domain, facilitating filament disassembly. This process is mediated by protein kinases A (PKA) and C (PKC), calmodulin (CaM)-kinase II, p21-activated kinase (PAK) and Cdc2 kinase (Ku et al., 2002; Snider and Omary, 2014). *S.* Typhimurium effector SptP is a tyrosine phosphatase that can de-phosphorylate vimentin to make it more flexible (Murli et al., 2001). Both SptP and vimentin are recruited to membrane ruffles formed by the actin cytoskeleton (Fig. 3) (Fu and Galán, 1998; Kraxner et al., 2021; Murli et al., 2001). HopQ is an effector protein of the plant bacterial pathogen *Pseudomonas syringae* pv. *tomato* (*Pst*). Overexpression of HopQ enhances its interaction with vimentin, allowing vimentin to be degraded by p62-dependent selective autophagy. Attenuation of vimentin expression by HopQ inhibits the motility and metastasis of melanoma *in vivo* (Park et al., 2020). Together, these findings suggest that bacteria-induced remodeling of vimentin and its related signaling pathways influence the fate of host defense processes as well as of tumor progression.

Conclusions and perspectives

Vimentin, with its different subcellular localizations, exerts a number of roles during bacterial infection. First, cytoplasmic vimentin mainly works in two ways after cell invasion – bacteria utilize vimentin-coated vacuoles for their intracellular transportation, allowing them to escape from immune surveillance and lysosomal phagocytosis (Guignot and Servin, 2008; Kumar and Valdivia, 2008; Truchan et al., 2016). In addition, cytoplasmic vimentin activates inflammasomes and inflammatory cells upon bacterial infection (Dos Santos et al., 2015; McDonald-Hyman et al., 2018; Mor-Vaknin et al., 2013; Rivera, 2019; Su et al., 2019a; Su et al., 2019b). Second, cell-surface-exposed vimentin mediates bacterial invasion by serving as either a receptor, co-receptor or simply as a preferred landing site (Beninati et al., 2019; Chi et al., 2012; Chi et al., 2010; Deng et al., 2019; Ghosh et al., 2018; Zou et al., 2006). Moreover, CSV also participates in the transmission of pathogen invasion signals by acting as a scaffold for PRR, influencing inflammatory response (Henderson et al., 2012; Stevens et al., 2013). Finally, secreted vimentin has several roles in inflammatory responses, such as promoting the bactericidal function of macrophages (Mor-Vaknin et al., 2003), and reducing the tropism and adhesion of neutrophils, thereby reducing ALI (Lam et al., 2018).

When bacteria invade, they inject virulence factors into the host cytoplasm, which changes the fate of vimentin. Firstly, the expression of vimentin is altered, which leads to an EMT-like transition in infected cells (Abd-El-Raouf et al., 2020; Bessède et al., 2014; Fu et al., 2022; Marques et al., 2018; Tahoun et al., 2012; Wroblewski et al., 2015; Yu et al., 2014). Secondly, the dynamic assembly and disassembly of the vimentin network are coupled with bacterial infection (Coye and Collins, 2004; Icenogle et al., 2012; Ku et al., 2002), which is accompanied by increased bacterial susceptibility, cell differentiation and EMT (Krzysiek-Maczka et al., 2018; Lee et al., 2017; Tahoun et al., 2012; Thanaphongdecha et al., 2020).

In general, regardless of the intricate role in inflammation, vimentin favors bacterial binding and entry by directly serving as a receptor or co-receptor, or by interacting with bacterial proteins as a cell surface protein. Vimentin also assists bacterial trafficking and replication by aggregating around BCVs as a cytoplasmic protein

(summarized in Table 1). Strikingly, vimentin also tends to favor viral binding and entry, fusion and replication (Gladue et al., 2013; Nédellec et al., 1998; Pagani et al., 2017; Zhang et al., 2015; Zhang et al., 2021), suggesting a potentially conserved feature in both bacterial infection and viral infection. Especially, converging evidence shows that vimentin plays two distinct roles in COVID-19, not only being involved in the viral infection but also in the associated life-threatening lung inflammation (Li et al., 2020). Moreover, we have previously shown that vimentin serves as a structural organizer and an RNA-binding protein regulator to facilitate Zika virus (ZIKV) replication (Zhang et al., 2022), where we observed substantial reorganization of vimentin surrounding and protecting the ZIKV replication factory. Taken together, all these considerations strongly suggest that vimentin represents a valuable therapeutic target not only in bacterial infections but also in infections more broadly (Zhang et al., 2021), and molecules downregulating vimentin or suppressing the aggregation of vimentin to the pathogen-containing vacuole are promising for treatment of broad-spectrum pathogen infection.

In conclusion, although vimentin has been shown to be important in a number of bacterial infections, its regulatory role and exact molecular mechanisms need to be further elucidated. This will undoubtedly improve our knowledge of pathogen–host interactions, which is necessary if vimentin is to be considered as a potential therapeutic target.

Competing interests
The authors declare no competing or financial interests.

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