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Vitronectin in host pathogen interactions and antimicrobial therapeutic applications

Mini-Review

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Abstract: Vitronectin (Vn) is a multifunctional glycoprotein profusely present in serum and bound to epithelial cell surfaces. It plays an important role in cell migration, tissue repair and regulation of membrane attack complex (MAC) formation. In the last decade the role of Vn has been extensively investigated in eukaryotic signalling and cell migration leading to the possibility of developing novel anticancer drugs. In parallel, several studies have suggested that pathogens utilize Vn in invasion of the host. Here we review the properties of Vn and its role in host-pathogen interactions that might be a future target for therapeutic intervention.

Keywords: *Bacteria • Complement system • Extracellular matrix • Innate immunity • Integrins • Vitronectin*

1. Introduction

Vitronectin (Vn) is a multifunctional glycoprotein that ensures optimum homeostasis in the body by regulating angiogenesis, cell migration and tissue repair [1]. However, it also plays an important role in tumor growth and metastasis [2], atherosclerotic disease [3] and viral infections [4]. Vn is an effective regulator of the complement system that limits the self-reactivity of the membrane attack complex (MAC) in the host. There are also other complement regulators, such as the classical complement pathway regulator C4b binding protein (C4BP) that binds to C4b followed by degradation of C4b with the help of factor I, and finally degrades C3 convertase. Additionally, factor H (FH) inhibits the activation of the alternative complement activation pathway by binding to factor C3b and inactivating it in the presence of factor I [5]. Activation of the complement system by the classical, alternative, or lectin-mediated pathways leads to a common lytic pathway after C5b activation. Subsequently, a C5b-C7 complex is formed and immobilized on the bacterial surface by C8. The C5b-C8 complex is recognized by C9 and results in C9 polymerization to form a cytolytic pore. Vn inhibits the association of C5b-C7, and suface-bound Vn may bind the C5b-7 complex that consequently does not associate with C8 for the initiation of the MAC. In addition, Vn bound to the bacterial surface may also remain active to interact with C9 and inhibit C9 polymerization.

The major complement regulators described above are frequently recruited by bacterial pathogens at their surfaces in order to circumvent the host innate immune response [5]. Since the first discovery of an interaction between Vn and pathogens by Chhatwal and co-workers in 1987, the role of Vn in microbial pathogenesis has been widely appreciated and investigated [6]. Of note, a large body of studies has suggested the pivotal role of heparin binding domains (HBDs) of Vn in the interaction with pathogens. Three distinguished HBDs have been defined on the Vn molecule, residing at the amino acids 82-137 (HBD-1), 175-219 (HBD-2), and finally 348-361 (HBD-3), The most C-terminal one, HBD-3, has been characterized as the major binding site recognised by pathogens [7] as illustrated in Figure 1.

Vitronectin initiates cellular signaling by interacting with integrins (α3β1, αvβ1, αvβ3, αvβ5 and αIIbβ3) at its N-terminal region containing the amino acids RGD. Binding of fibronectin and Vn induces integrin clustering and recruitment of host proteins involved in the signalling cascade, resulting in actin rearrangement

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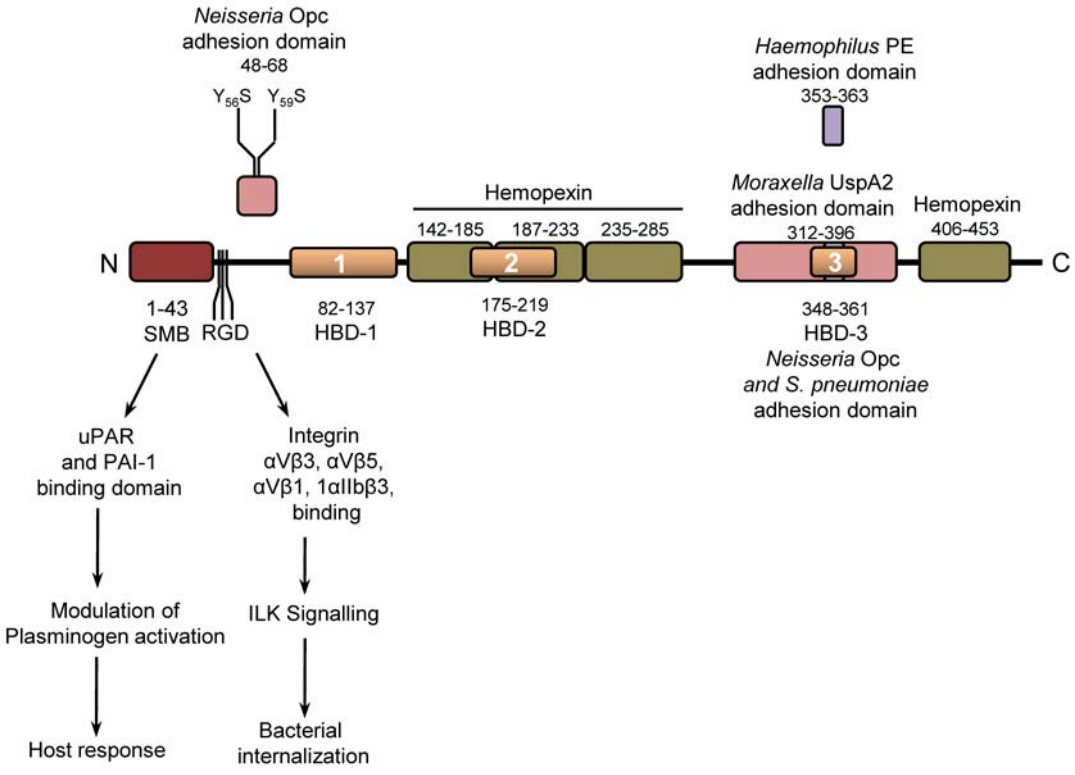

Figure 1. Vn has a multidomain structure, wherein the N-terminal somatomedin-B (SMB) domain (amino acids 1-43) is involved in functional regulation by binding to the plasminogen activator inhibitor-1 (PAI-1). This interaction controls the activity of the plasminogen system to limit the overall damage of tissues. Bacterial pathogens degrade the PAI-1/Vn complex in order to accelerate plasmin activity and thus enhance the tissue damage. Downstream of the SMB domain is a Arg-Gly-Asp (RGD) sequence that recognises integrins and is involved in signalling mediated by the integrin-linked kinase (ILK). Bacterial pathogens can be internalized by host cells using this mechanism. Furthermore, Vn has four putative hemopexin-like domains (green colour). There are three distinguished heparin binding domains (HBDs) spanning amino acids 82-137, 175-219, and 348-361 in the Vn molecule. *Strep. pneumoniae* binds to the region HBD-3 (unpublished data). This interaction helps in bacterial adhesion and internalization mediated by Vn-integrin signalling. *M. catarrhalis* is also known to bind at the region 312-396 and utilizes Vn at its surface to inhibit the MAC. In addition, *H. influenzae* interacts with HBD-3 at the amino acid region 353-363. This interaction leads to MAC inhibition and an increased bacterial survival in normal human serum. *N. meningitides* utilizes Vn recruitment for serum resistance as well as internalization. This species is known to bind to the HBD-3 region, but also to the N-terminal domain 48-68, in particular to the sulphated residues of Y56 and Y59. Moreover, *Strep. pyogenes* has multiple binding sites on Vn (the hemopexin domains) in addition to the C-terminal HBD [38,68].

and internalization of the Vn-integrin complex. Pathogens therefore bind Vn and manipulate the interaction for adherence on epithelial cells as well as for internalization into host cells [8,9]. The role of Vn in bacterial pathogenesis has been comprehensively described in our recent publication [7]. In the present review, we highlight the molecular aspects of Vn in host-pathogen interactions and further conclude its therapeutic application in antimicrobial therapy.

2. Molecular forms of vitronectin

Vn exists in two isoforms with molecular weights of 75 kDa and 65 kDa. The circulating form of Vn is usually present as a monomer (native Vn) that represents approximately 93% of the total Vn content in human plasma. The remaining 2 to 7% is activated Vn and undergoes a unique conformational change resulting in a multimeric form [10]. It was initially believed that native Vn does not have a heparin-binding capacity due to the cryptic HBD found in native Vn [11]. This is in bright contrast to other ECM proteins, *e.g.*, fibronectin that has a heparin-binding capacity even at its native conformation. However, Zhuang and co-workers (1997) discovered that monomeric Vn also binds heparin *in vitro*, while increased binding was observed with the activated form [12]. Moreover, the heparin-binding property of multimeric Vn involves ionic interactions [12]. The most common protocol used in the purification of Vn from serum is based upon denaturing conditions in the presence of urea. Exposure to urea and subsequent renaturation causes multimeric associations

of Vn molecules, resulting in multiple heparin-binding sites [13].

Native (monomeric) Vn is involved in the regulation of plasminogen activation by interacting with plasminogen activator inhibitor-1 (PAI-1) and urokinase plasminogen activator (uPA)/uPA receptor (uPAR). This interaction leads to Vn multimerization that in turn increases Vn efficiency to bind with the surface receptor of epithelial cells and promote other eukaryotic functions [14,15]. Of note, only multimeric Vn can bind to the epithelial cell surfaces and induce cell signalling [10,13], and in some cases the glycoprotein is also endocytosed. PAI-1 and heparin both promote multimerization of the Vn molecule, but their mechanism of interaction and impact on the production of multimeric Vn is different [16]. Conformational transitions of the Vn molecules as described above are solely concluded from *in vitro* studies. In contrast, the generation of multimeric Vn from monomers is only partially known *in vivo*. It thus remains to investigate whether activated Vn occurs under continuous exposure to its ligands, such as PAI-1 and glycosaminoglycans, or whether the *in vitro* induced multimerization of Vn resembles the *in vivo* conditions.

In the complement system, Vn regulates the self-reactivity of the MAC by inhibiting the C5b-7 complex assembly and C9 polymerization. It is, however, an enigma whether the regulation of the MAC is conducted by a specific conformation of Vn. In some experimental models it has been shown that injection of [^{32}P]-labelled monomeric Vn into mice leads to incorporation of radioactive Vn into a high molecular weight soluble (S) C5b-9 complex, whereas injection of urea-activated [^{32}P]-labelled polymeric Vn is rapidly cleared from serum [17]. In general it is thus believed that monomeric Vn performs its MAC inhibitory role by making a soluble Vn/C5b-7/C5b-8/C5b9 complex. These complexes are lytically inactive, unable to be inserted into the cell membrane, and finally cleared from the circulation [17]. The role of polymeric Vn in the regulation of MAC is yet to be defined. On the other hand, it has been observed that only polymeric (activated) Vn is importantly associated with bacterial pathogenesis during adhesion to host epithelial cells. Recently, it was observed that adhesion and internalization of *S. pneumoniae* to lung epithelial cells is several-fold increased in the presence of polymeric Vn compared to native Vn [8]. More recently, similar observations have been noticed with *Neisseria meningitidis*, where only activated Vn enhanced bacterial adhesion and internalization of HBMEC cells [9]. These studies suggested that the polymeric Vn has a suitable conformation that makes a bridge between epithelial cells and the pathogens. Thus, the polymeric form of Vn that consists of the minor fraction of total Vn (2 to 7%) might be a limiting factor for many pathogens to acquire Vn-mediated serum resistance or adherence. Hence, accurate estimation of the availability of Vn to pathogens during infection can only be achieved by using *in vivo* models.

3. The PAI-I/Vn complex and bacterial pathogenesis

Vn is unique among other extracellular matrix (ECM) proteins, considering its role as an effective regulator of the fibrinolytic system. This is achieved by binding of Vn to plasminogen activator inhibitor (PAI-1). The PAI-1/Vn complex inhibits the plasminogen activity by inactivating tissue plasminogen activator (tPA) and urokinase plasminogen activator (uPA) [18]. Vn increases the half-life of PAI-1 by 2- to 4-fold, thus prolongs inhibitory activity of PAI-1 on the activation of plasminogen [19]. It has been shown in a mouse model that PAI-1 expression is necessary to protect the host from Gram-negative pathogens by recruiting neutrophils to the alveolar compartment. PAI-1 knockout animals are prone to infection by *Klebsiella pneumoniae,* and restoring the expression of PAI-1 in these knockout models generates resistance against *K. pneumoniae* infection [20]. Similarly, the role of PAI-1 in bacterial pathogenesis is also supported by the increased level of the plasminogen inhibitor during sepsis and other severe pathological conditions [21-23]. Some bacterial pathogens such as *Pseudomonas aeruginosa*, *Staphylococcus aureus*, and *Bacillus subtilis* cause degradation of PAI-1 during invasion [24-26]. Bacterial proteases also degrade Vn during invasion [27,28], but there is no information available on degradation of the PAI-1/Vn complex. Recently it was shown that proteins of the omptins family (bacterial surface proteases) including plasminogen activator (Pla) of *Yersinia pestis*, PgtE of *Salmonella typhimurium*, and Kop of *K. pneumoniae* can degrade the PAI-1/Vn complex *in vitro* [19]. It has been hypothesized that abolished regulation of the tPA/uPA activity is attributed to the pathogen-dependent degradation of PAI-1/Vn complex and eventually lead to the uncontrolled fibrinolysis. Thus, a high production of plasmin will accelerate tissue damage that would be beneficial to the pathogens during invasion (Figure 1).

4. Interactions between bacterial pathogens and vitronectin

The well-studied complement regulators (C4BP, FH and Vn) are frequently recruited by bacterial

pathogens to circumvent the host innate immune response [29]. During the bacterial infection only one or all complement pathways will be activated, depending on the surface molecule of the infecting pathogen. In contrast to FH and C4BP, Vn inhibits the lytic (terminal) pathway that is ultimately common amongst all the complement pathways. Recruitment of Vn at the bacterial surface might thus be a more effective strategy compared to the other two complement regulators.

The MAC complex is more effective in killing of Gram-negative bacteria. This is in bright contrast to Gram-positive pathogens that are shielded against complement due to a thick peptidoglycan layer. Both Gram-positive and Gram-negative pathogens have, however, the capacity to bind Vn and utilize the molecule for inhibition of the MAC and/or adhesion to host tissues. The Gram-negative *H. influenzae*, for example, recruits Vn by the surface exposed adhesin protein E (PE), and *Haemophilus* surface fibrils (Hsf) [30-32], whereas *H. ducreyi* binds Vn by the protein DsrA [33]. On the other hand, *Moraxella catarrhalis* interacts with Vn by ubiquitous surface protein (Usp) A2 [7,34,35]. *N. meningitidis* [9], and *N. gonorrhoeae* [36] also acquire serum resistance by attracting Vn. Several other Gram negative bacterial pathogens bind Vn, but the importance of these interactions in serum resistance have not been explored in detail [35].

Similarly, Gram-positive pathogens, *e.g.*, *Streptococcus pneumoniae*, *Strep. pyogenes*, *Strep. bovis*, *Strep. suis*, *Strep. dysgalactiae*, *Staph. epidermidis*, *Staph. aureus* and *Enterococcus faecalis* bind Vn and utilize the protein for adhesion to host epithelial surfaces. Details of these pathogens and their interactions with Vn have recently been reviewed [7]. The inhibitory capacity of Vn regarding the MAC and Gram-positive pathogens have not been reported until now. However, the role of Vn-dependent bacterial adhesion and internalization into host cells has been thoroughly explored. It is well known that several invasive pathogens utilize integrin-mediated internalization by using host phagocytic mechanisms [37]. Vn binds to epithelial cell surface integrin receptors (αvβ3, αvβ1, α3β, 1αIIbβ3 and αvβ5) *via* RGD-binding motifs, where vitronectin and integrin receptors interacts to induce signalling by multiple pathways [35].Thus, during adhesion bacteria will only successfully cross-link Vn that has the ability to bind epithelial surface receptors. Similarly, host epithelial surface-bound Vn will only be recognised by bacteria if the pathogen binding sites on the Vn molecule are available for interaction.

5. Vitronectin and future therapeutic applications

The biological functions of Vn are associated with its conformation either in an unfolded (activated) or folded (native) form. However, activated Vn is highly associated with bacterial pathogenesis during infection as well as in tumor metastasis, which is mainly attributed to its frequent distribution in ECM or on epithelial cell surfaces, a preferable platform for both bacterial colonization and cancer cell invasion. Microbes bind Vn and utilize the molecule to establish infection such as to subvert host complement killing, adherence to host epithelial cells followed by internalization through Vn-integrin signaling [7]. Most of pathogenic bacteria bind to activated Vn, particularly either at the N-terminal polyanionic region (between amino acids 43-68) [9], the central domain containing hemopexin like domains (comprising residues 131-323) [38], or at the basic carboxy terminal HBD-3 [7]. The bacterial-Vn binding usually does not interfere with the Vn domain involved in the inhibition of C5b-9 complex (internal region between amino acid 51-310), thus allowing the complement regulator to remain active in inhibiting MAC formation while binding on the bacterial surface [30,39,40]. HBD-3 was proposed to be involved in the inhibition of the MAC [41]. However, the inhibitory domain was later relocated as described above [39,40].

Interestingly, antimicrobial peptides (AMP) including LL37 and α-defensin share similar heparin binding motifs as seen in HBD-3 [42,43]. These AMPs lose their bactericidal properties when interacting with glycosaminoglycans. Several cationic peptides representing the heparin binding domain of fibronectin, various laminin isoforms, von Willebrand factor, Protein C inhibitor as well as C3 show antimicrobial effects [44,45]. HBD-3 of Vn which consists of Cardin motifs (XBBXBX, where X represents hydrophobic or non-polar amino acids and B represents basic amino acids) [46,47] was bactericidal towards *E. faecalis* at concentrations between 0.6 to 3 μM, a killing effect which is comparable to the classical LL37-defensin. At low salt conditions in a radial diffusion assay, HBD-3 (100μM) showed a more potent antibacterial activity to *Escherichia coli*, *Candida albicans*, *P. aeruginosa* and *Proteus mirabilis* as compared to the defensin LL37. However, the actual mode of action of antibacterial activity of the HBD-3 remains unknown, instead more work is needed to expand the understanding of the utilization of Vn as an AMP. To date, reports concerning the exploration of Vn peptides as antimicrobial agents are still limited.

Bacterial colonization on commonly used biomaterial implants and medical devices causes serious complications. For example, implant-associated infections have caused a high mortality among patients with heart implants, and serious disabilities in patients with orthopaedic devices [48,49]. Relative immune system fitness of the implant recipient and virulence of microorganisms such as the capacity to form biofilm are the main factors contributing to infections on implant surfaces. When a biomaterial is implanted and exposed to blood, a reservoir of host proteins including fibrinogen, Vn, fibronectin, albumin and immunoglobulins usually tends to adsorb to its surface. Moreover, Vn and fibronectin adsorbed on foreign surfaces unfold and activate glycoproteins, and potentially increases interactions with their ligands and bacterial specific receptors [50,51]. Thus, the thin layer of host proteins would favour the interaction of microbes with the proteinous film, and the microbes would consequently use specific receptors through hydrophobic interactions or Van der Waals and electrostatic charges, facilitating the formation of biofilm. In the presence of cerebrospinal fluid (CSF), Vn was found to mediate adherence of coagulase-negative staphylococci on polyvinylchloride (PVC), a material used in prosthetic devices [52]. The biofilm on biomaterial surfaces is usually resistant to antibiotic killing and infection can often only be eradicated by the removal of the infected biomaterial. Therefore, several strategies have been developed to control the biofilm related to implant-associated infections, such as i) by using non-protein adsorptive surfaces [53,54], ii) pre-colonization of surfaces with non-pathogenic bacteria for nich masking [55], iii) coating of antibiotics [53,56,57], and iv) surfaces containing biocidal substances [58,59]. Providing the advantages of the stability *in vivo* of AMP and lack of resistance development, pre-coating biomaterial surfaces with antimicrobial agents including HBD-3 of Vn would be an effective effort to prevent biofilm formation, and would in the long run reduce survival of microorganisms. Several antimicrobial coating strategies have recently been reviewed in detail [60]. In addition, it is possible to reduce bacterial adherence to biomaterial surfaces by targeting activated Vn with specific antibodies to the biomaterial surface after immediate exposure to body fluids containing Vn [61,62]. A Vn-binding *Staph. epidermidis* showed reduced binding to PVC of prosthetic devices when the PVC priorly exposed to CSF was incubated with anti-Vn antibodies [52,63].

In contrast to AMP derived from Vn, the full length Vn molecule has not been shown to exert any bactericidal effect, instead Vn exhibits a role as a pro-bacterial pathogenesis molecule. However, Vn is a potent inhibitor of complement activation that is prone to occur at the biomaterial surface in implant devices that are in contact with blood and aqueous humor [64,65]. Complement activation in the vicinity of an implant results in unspecific inflammation and attachment of thrombocytes, bacteria and fungi. Intriguingly, the complement inhibitory role of Vn at the biomaterial surface is fazed by the presence of Vn-binding microorganisms [66,67]. Binding of the Vn-binding *Staph. hemolyticus* to surfaces precoated with the glycoprotein results in hindrance of Vn from inhibiting complement activation. Conversely, interaction of non-Vn binding strains of *Staph. epidermidis* with surface-coated Vn does not affect the complement-inhibitory role of Vn.

6. Conclusions

Vn functions as one of the major host factors that governs multiple biological processes. The regulatory mechanisms by Vn in cellular migration have been targeted for the development of anticancer therapeutics. In addition, this glycoprotein has also been recognized as a biomarker molecule in pathophysiological processes. The adhesive and MAC inhibitory properties of Vn is utilized by pathogens for adherence to host cells and protection against the innate immune system. Moreover, some bacterial pathogens have also manipulated the Vn-integrin mediated signalling pathway to achieve internalization/invasion. In a nutshell, the Vn-host interaction could be targeted for the development of novel antimicrobial agents. In addition, heparin-binding Vn peptides can be used as antibacterial agents on implant devices or in antiseptic formulations. The implementation of the Vn antimicrobial peptides or inhibitors to prevent Vn interactions with pathogens will thus shed light on alternative drugs to overcome the issue of antibiotic resistance. Such development requires careful consideration and configuration based on targeted anatomical sites, taking into account the multi-essential role of Vn for host physiological needs.

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