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Review Article

Bacterial Plasminogen Receptors: Mediators of a Multifaceted Relationship

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Multiple species of bacteria are able to sequester the host zymogen plasminogen to the cell surface. Once localised to the bacterial surface, plasminogen can act as a cofactor in adhesion, or, following activation to plasmin, provide a source of potent proteolytic activity. Numerous bacterial plasminogen receptors have been identified, and the mechanisms by which they interact with plasminogen are diverse. Here we provide an overview of bacterial plasminogen receptors and discuss the diverse role bacterial plasminogen acquisition plays in the relationship between bacteria and the host.

1. Introduction

Recruitment of plasminogen to the bacterial cell surface is emerging as a central theme in host/pathogen interactions. The glycoprotein plasminogen is found in plasma and extracellular fluids at concentrations of approximately 2 μM. Upon activation, plasminogen is converted to the serine protease plasmin [1]. Plasmin is able to degrade fibrin clots, connective tissue, extracellular matrix (ECM), and adhesion proteins. Plasmin itself contributes to a number of amplification loops which leads to increased plasminogen activation. Plasmin-mediated proteolysis of cell membrane proteins exposes cryptic plasminogen-binding sites within receptors, subsequently enhancing the recruitment of plasminogen to cell surfaces [2]. Similarly, cleavage of the inactive form of the urokinase plasminogen activator pro-uPA by cell bound plasmin generates the active two-chain uPA. This feedback activation results in a significant increase in plasmin activation within biological systems [3]. Additionally, activation of prometalloproteases by plasmin results in degradation of the collagen structural components of the ECM, leading to widespread tissue destruction. Recruitment of plasminogen to the surface of bacteria by specific plasminogen receptors was first reported over 20 years ago [4]. Since then, the importance of this interaction in bacterial virulence has become the focus of a large body of research. It is now clear that recruitment of plasminogen to bacterial cell surfaces is a feature common to both pathogenic and commensal bacteria. This paper provides an overview of known bacterial plasminogen receptors and examines the diverse roles they play in the host-bacteria interaction.

2. Plasminogen

Plasminogen is the inactive zymogen form of the enzyme plasmin [5, 6]. Posttranslational processing results in several different forms of plasminogen (Figure 1). The circulating mature form of plasminogen is known as Glu-plasminogen as a consequence of the glutamic acid residue at the N-terminus. Glu-plasminogen consists of the preactivation peptide followed by five characteristic kringle domains and then the serine protease active site in the C-terminal region [6] (Figure 1). The amino acid residues His^{603}, Asp^{646} and Ser^{741}, make up the catalytic triad of the serine protease domain. This domain catalyses the hydrolysis of peptide bonds, resulting in peptides with C-terminal arginine and lysine residues [6]. The kringle domains of plasmin(ogen) mediate interactions with multiple ligands, including fibrin(ogen) and mammalian cellular plasmin(ogen) receptors

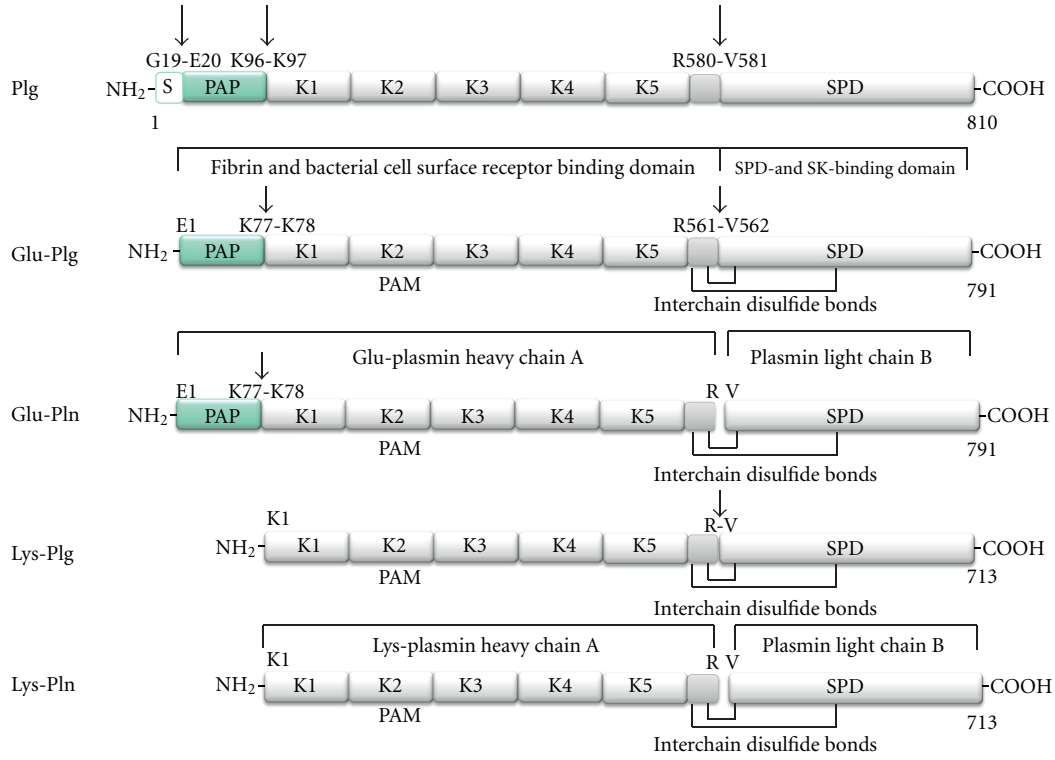

Figure 1: Structural domains of human plasmin(ogen) forms. Human plasminogen is synthesised as an 810 amino acid protein. The 19 amino acid residue signal sequence is removed resulting in the circulating mature form (791 amino acids, ~90,000 kDa) known as Glu-plasminogen (Glu-plg) as it contains an N-terminal glutamic acid. Glu-plg contains a hairpin-loop structure called the PAN domain encompassing the preactivation peptide (PAP), followed by 5 homologous kringle domains (K1–K5) containing three intradomain disulfide bridges, followed by a peptidase S1 domain (SPD). The preactivation peptide is generated by plasmin cleavage giving rise to Lys-plg (713 amino acids, ~80,000 kDa). The conversion of Glu-plg or Lys-plg to their respective plasmin forms occurs by hydrolysis of the Arg-Val peptide bond shown by either uPA or tPA, yielding chain A and the smaller chain B, which remain covalently associated by interchain disulfide bonds. Kringles 1, 2, 4, and 5 contain lysine-binding sites (LBS) with affinity for free lysine and lysine-like compounds such as ω-aminocarboxylic ligands in the following order of binding affinity K1 > K4 > K5 > K2 [8]. Kringle 3 shows no detectable binding to Lys or Lys-like compounds [9], related to a sequence variation in its LBS. Glu-plg thus binds to various lysine-containing proteins via Kringles 1, 2, 4, and 5. Streptokinase (SK) and staphylokinase (not shown) bind in a 1 : 1 complex with the SPD to generate an activator complex. Not shown: Mini plasminogen (K5 plus the SPD) can also be generated by stromelysin-19 cleavage of the Pro466-Val467 bond of Plg. Sequence data are derived from UniProt (swiss-prot entry P00747). Plasminogen (EC = 3.4.21.7) (http://www.uniprot.org/uniprot/P00747).

[7]. In particular Kringles 1, 2, 4, and 5 (K1-K5) contain lysine-binding sites (LBS) comprised of a hydrophobic cleft formed by aromatic residues that most commonly bind C-terminal lysine residues and internal lysine residues of receptors. As described in Figure 1, the kringles show differing affinities for free lysine and lysine-like compounds such as ω-aminocarboxylic ligands, in the following order of binding affinity K1 > K4 > K5 > K2 [8]. Kringle 3 shows no detectable binding to Lys or Lys-like compounds [9]. Intramolecular binding between lysine residues and the LBS of these Kringles maintains Glu-plasminogen in a closed conformation which is less susceptible to activation [6, 10]. Competitive binding interactions with fibrin(ogen) or plasminogen receptors allows Glu-plasminogen to adopt an open conformation, exposing the activation loop (Arg^{561}-Val^{562}) to cleavage by specific mammalian plasminogen activators thus forming Glu-plasmin [6, 7] (Figure 1). Alternatively, cleavage of the Lys^{77}-Lys^{78} peptide bond may also occur leaving the plasminogen molecule with a Lys residue at the-N terminus (Lys-plasminogen) [6] (Figure 1). Lys-plasminogen has a more open, U-shaped conformation than Glu-plasminogen making it more readily activated to Lys-plasmin by the plasminogen activators [11, 12]. The resulting two-chain Glu- or Lys-plasmin molecule consists of the plasmin heavy chain A in the N-terminal region and the plasmin light chain B in the C-terminal region held together by interchain disulfide bonds (Figure 1).

Two differentially glycosylated variants of human Glu-plasminogen exist. Both variant 1 and 2 contain O-linked glycosylation site, whereas variant 1 contains an additional N-linked glycosylation site (located at Asn^{289} within Kringle 3) [13–15]. These glycosylation patterns appear to affect both the stability and affinity of the protein to interact with lysine moieties as well as its subsequent activation rate [16]. Differences in glycosylation were recently shown to affect the positioning of Kringle 3 (a non-LBS containing Kringle) in the X-ray crystal structure of plasminogen, which has consequences for efficient Glu-plasminogen activation [10].

3. Plasminogen-Binding Bacteria

Commandeering the host plasminogen activation system is a common mechanism employed by a variety of bacteria [17–20]. The ability to acquire cell surface plasminogen is not host species restricted or limited to specific sites of infection. Rather, the ability to recruit plasminogen is emerging as a central theme in the interaction between host and bacteria. Early studies by Ullberg et al. showed that 5 out of 11 species of gram-negative bacteria tested and 9 out of 17 species of gram-positive bacteria tested displayed a specific and high affinity interaction with Glu-plasminogen [21, 22], although plasminogen acquisition by different strains within each species varied significantly. Many studies have since focused on the ability of highly pathogenic bacteria to interact with plasminogen, including *Streptococcus pyogenes*, *S. pneumoniae*, *Staphylococcus aureus*, *Helicobacter pylori*, *Mycobacterium tuberculosis*, *Neisseria meningitides,* and *N. gonorrhoeae,* [23–25]. There is also a growing body of evidence to indicate that animal pathogens sequester plasminogen. Examples of this include *Mycoplasma hyopneumoniae* and *M. gallisepticum* which bind porcine and chicken plasminogen, respectively, [26, 27] and the canine pathogen *S. suis* [28].

Interactions with plasminogen are not solely the domain of pathogenic bacteria, with a number of commensal species also reported to bind plasminogen with both high affinity and specificity, including several species of oral *streptococci* [29], *bifidobacteria* [30], and *lactobacillus* [31]. The role of bacterial-plasminogen recruitment in pathogenesis will be discussed in more detail later; however, given the above findings it appears that plasminogen recruitment by bacteria may have a multifaceted role in the interaction with the host. This may underlie the diversity of plasminogen receptors expressed by bacteria and the different mechanisms of interaction which have been described to date.

4. Bacterial Plasminogen Receptors

Recruitment of plasminogen to the bacterial cell surface is mediated directly by either specialised cell surface receptors or cytoplasmic and glycolytic pathway proteins localised to the bacterial cell surface or indirectly via interactions with host plasma proteins such as fibrinogen. Table 1 gives an overview of the most well-characterised bacterial plasminogen receptors.

4.1. Specialised Cell Surface Receptors. Cell surface expressed receptors can be defined as those proteins which have a recognisable N-terminal signal sequence and membrane anchor motif. Several cell surface expressed plasminogen receptors have been well characterised, and it is interesting to note that many of these appear to have internal plasminogen-binding sites. Among the best characterised of these is the group A streptococcal plasminogen binding M protein. This coiled-coil alpha helical protein extends from the streptococcal cell surface and binds Glu-plasminogen with an affinity of K_d 1-2 nM [32, 33]. A combination of bacterial mutants, synthetic peptides and amino-acid substitution in recombinant proteins has been utilised to demonstrate that plasminogen binding to group A streptococcal M proteins is dependent on the presence of an internal plasminogen-binding repeat domain, consisting of positively charged arginine and histidine residues [34–36]. X-ray crystallography studies of the interaction between a 30-amino acid peptide comprising the plasminogen binding domain of streptococcal M protein (VEK-30) and a modified version of K2 of plasminogen indicate that Arg^{17} and His^{18} of VEK-30 form a pseudolysine structure that interacts with the LBS of this kringle [36]. This work supports earlier studies which showed that group A streptococcal plasminogen-binding M proteins interact with K2 of plasminogen, which contains a low affinity lysine-binding site [37]. Despite the fact that plasminogen binding by M proteins is readily inhibited by the lysine analogue EACA [32], mutation of the lysine residues within the bacterial interaction motif is not sufficient to fully abrogate plasminogen binding [34]. This highlights the important point that EACA competition alone is insufficient to demonstrate the role of lysine residues in interactions with plasminogen and its many receptors. Rather, the ability of lysine analogues to compete out plasminogen binding can be interpreted as demonstrating a role for the LBS within the kringle domains of plasminogen.

Plasminogen-binding M proteins are expressed by approximately 15% of group A streptococcal isolates, and similar proteins have been identified in a variety of group C and G streptococcal strains [38, 39]. Recently, a plasminogen-binding M protein expressed by the group G streptococci *S. canis* was reported to bind to miniplasminogen, a plasminogen variant consisting of only K5 and the serine protease domain [28]. Similarly, the M-like protein of group C streptococcus GCS3 likely interacts with K4 or K5 of plasminogen [40]. K4 and K5 show a high affinity for lysine-based ligands when compared with K2 [8], so, whilst specific plasminogen-binding sites within the M proteins of group C streptococcus and *S. canis* are yet to be defined, it is likely that they display markedly different properties to the internal motif described for the group A streptococcal plasminogen-binding M proteins. It is possible that these receptors mediate plasminogen binding at different sites or stages of infection; however, this hypothesis has yet to be fully explored. Based on the crystal structure of plasminogen, it has been suggested that the interaction of K5 with lysine residues is key to the structural change of plasminogen from its closed to open form [41]. It is tempting to hypothesise that bacteria which do not express their own plasminogen activators, such as *S. canis* may have evolved plasminogen interaction mechanisms that allow more efficient activation by host activators.

Internal plasminogen-binding sites have also been proposed for several bacterial lipoproteins identified as plasminogen receptors. *B. burgdorferi* binds plasminogen via an array of lipoproteins, including ErpP, ErpC, Erp, and OspA [46], while *B. recurrentis* and *B. hermsii* mediate plasminogen binding by the lipoproteins HcPA and BhCRASP1 [87, 88]. Similarly, several as yet uncharacterised lipoproteins of *Francisella tularensis* have been found to interact with plasminogen in human plasma via ligand blot analysis [89]. Whilst specific plasminogen binding sites within all

Table 1: Bacterial plasminogen receptors and their interactions with plasminogen.

Plasminogen receptor	Bacterial species	Cell surface attachment	Binding affinity (K_D)	Binding interactions and characteristics	References
Bfp60	*Bacteroides fragilis*	Anchored	ND	ND	[42]
Choline-binding protein E (CBPE)	*Streptococcus pneumoniae*	Anchored	ND	Binds plg via internal lysine residues K^{259}, K^{267}, and K^{319} present in the phosphorylcholine esterase domain.	[43, 44]
CRASP-1, 3, 4, and 5	*Borrelia burgdorferi*	Anchored	ND	ND	[45]
ErpP, ErpC, and ErpA	*Borrelia burgdorferi*	Anchored	Glu-plg: K_D = 25 nM	Plg binding is associated with C-terminal lysine residues. Bound plg can be activated by uPA.	[46]
Erp63	*Borrelia spielmanii*	Anchored	ND	ND	[47]
Flagella	*Escherichia coli*	Anchored	ND	ND	[48]
GlnA1	*Mycobacterium tuberculosis*	Anchored	ND	Interact with LBS within plg	[49]
LenA	*Leptospira interogans*	Anchored	ND	Interacts with the K1–K3 plg fragment	[46, 50]
Leptospiral surface adhesin Lsa66	*Leptospira interrogans*	Anchored	Plg: K_D = 68.8 nM	ND. Bound plg can be activated by uPA	[51]
Lp30	*Leptospira interrogans*	Anchored	Plg: K_D = 167.39 nM	ND. Bound plg can be activated by uPA	[51]
LIC12238	*Leptospira interrogans*	Anchored	Plg: K_D = 11.97 nM	ND. Bound plg can be activated by uPA	[52]
LIC10494			Plg: K_D = 10.98 nM		
LIC12730			ND		
LipL32, LipL40	*Leptospira interrogans*	Anchored		ND	[52]
Lp29, Lp49	*Leptospira interrogans*	Anchored		ND	[52]
Lsa20	*Leptospira interrogans*	Anchored	ND	ND	[53]
Lsa66			Plg: K_D = 68.8 nM		[51]
M and M-like protein	*Streptococcus pyogenes*	Anchored	Glu-plg: K_D = 1.6 nM–7.6 nM	K2	[34, 35]
	Streptococcus canis		Mini-plg: K_D = 2.7 nM	High affinity for plg K5	[28]
	Streptococcus equi		Plg: K_D = 18 nM	Plg binding not competed out by excess K1–3, but inhibited by EACA, suggesting a role for K4 or K5	[54]
Mhp 107	*Mycoplasma hyopneumoniae*	Anchored	Plg (porcine): K_D = ND	ND	[26]
MPL36	*Leptospira interrogans*	Anchored		ND	[52]
Outer surface protein A (OspA)	*Borrelia burgdorferi*	Anchored	Glu-plg: K_D = 260 μM	Interacts with LBS within plg and pln. Bound plg can be activated by both uPA and tPA	[55]
70 kDa surface protein (OppA)	*Borrelia burgdoferi*	Anchored	ND	ND	[55, 56]
PavB	*Streptococcus pneumonia*	Anchored	ND	ND	[57]
PfbB	*Streptococcus pneumonia*	Anchored	ND	ND	[58]
PfbA	*Streptococcus pneumonia*	Anchored	ND	ND	[59]
Plasminogen-binding protein (Pbp)	*Bacteroides fragilis*	Anchored	ND	ND	[60]
PbbA and pgbB	*Helicobacter pylori*	Anchored	ND	Interacts with LBS of plg	[61]

Table 1: Continued.

Plasminogen receptor	Bacterial species	Cell surface attachment	Binding affinity (K_D)	Binding interactions and characteristics	References
P116	*Mycoplasma hyopneumoniae*	Anchored	Asp-plg (porcine): K_D = 44 nM	ND	[26]
Protein E	*Haemophilus influenzae*	Anchored	ND	Interacts with LBS of plg	[62]
Type 1fimbriae	*Escherichia coli*	Anchored	Glu-plg: K_D = 200 nM	ND	[63, 64]
	Streptococcus pneumoniae		Plg: K_{D1} = 0.55 nM; K_{D2} = 86.2 nM	Residues 248–256; C-terminal lysyl residues LL^{433} and LL^{434}. Interacts with LBS within Plg	[65–67]
	Streptococcus pyogenes		Glu-Plg: K_D = 1.6 nM; Lys-plg: K_D = 127 nM	C-terminal lysine residues K^{434} and K^{434}; Residues 252–255. Interacts with LBS within Plg	[68, 69]
	Streptococcus suis		Plg: K_D = 14 nM	Contains internal nonapeptide motif	[70]
	Bifidobacterium lactis		Plg: K_D = 42 nM	Lysine and glutamic acid residues K^{251}, K^{251}, and E^{252}	[30]
	Bacillus anthracosis		ND	Plg binding partially mediated by C-terminal lysine. Interacts with LBS within Plg	[71, 72]
α-enolase	*Neisseria meningitidis*	Nonanchored	ND	Undefined internal plg-binding motif	[73]
	Streptococcus mutans		ND	Binds plg via C-terminal lysine	[74]
	Streptococcus agalactiae		Glu-Plg: ND; Lys-Plg: ND	ND	[75]
	Mycoplasma gallisepticum		ND	ND	[27]
	Mycoplasma fermentas		ND	ND	[76]
	Borrelia burgdorferi		Glu-plg: K_D = 125 nM	Interacts with LBS within Plg	[77]
Ag85B	*Mycobacterium tuberculosis*	Nonanchored	ND	Interacts with LBS within plg	[49]
Aspartase	*Haemophilus influenzae*	Nonanchored	ND	K4. Potent stimulator of tPA but not uPA	[78]
	Bifidobacterium animalis		Plg: K_D = 11.97 nM	Interacts with LBS within plg	[79]
DNaK	*Neisseria meningitidis*	Nonanchored	ND	Undefined internal plg-binding motif	[73]
	Mycobacterium tuberculosis		ND	Interacts with LBS within plg	[49]
Elongation factor-tu (EF-tu)	*Bacillus anthracosis*	Nonanchored	ND	Interacts with LBS within plg	[71]
Fructose-1,6-bisphosphate aldolase	*Mycoplasma tuberculosis*	Nonanchored	Plg: K_D = 6.73 nM	ND	[80]
	Streptococcus pneumoniae		Pln: K_{D1} = 28 nM; K_{D2} = 52 nM Plg: K_{D1} = 0.43 μM; K_{D2} = 0.16 nM	Binds plg via two C-terminal lysine residues separated by isoleucine and alanine	[67, 81]
Glyceraldehyde 3-phphate dehydrogenase (GAPDH; GAPC; SDH; Plr)	*Streptococcus pyogenes*	Nonanchored	ND	ND	[82]
	Bacillus anthracis		Plg: K_D = 78.5 nM; 572 nM	ND	[83]
	Streptococcus equisimilis		Plg: K_D = 220 nM; Pln: K_D = 25 nM	ND	[84]
Peroxiredoxin	*Neisseria meningitidis*	Nonanchored	ND	Undefined internal plg-binding motif	[73]
Phosphoglycerate kinase	*Streptococcus equisimilis*	Nonanchored	ND	Shown to bind both plg and pln	[85]
SkzL	*Streptococcus agalactiae*	Nonanchored	Glu-plg: K_D = 3−16 nM; Lys-plg: K_D = 80 nM; Pln K_D = 50 nM	ND	[86]

ND: not determined, plg: plasminogen, pln: plasmin, LBS: lysine binding site, K1–5: kringle 1–5.

these proteins have not been fully defined, the role of C-terminal lysines appears limited for those that have been characterised. Truncated Erp proteins lacking three native C-terminal lysine residues show only a partial reduction in plasminogen binding, supporting a role for both C-terminal lysine residues and an unidentified internal binding site in the interaction with plasminogen [46]. Similarly, mutation of residues Lys^{259}, Lys^{267}, and Lys^{319} within the choline-binding protein E (CBPE) of *S. pneumoniae* results in a 70% reduction in plasminogen when compared to the wild-type protein [43]. A number of other receptors with less well-defined plasminogen-binding sites are listed in Table 1.

4.2. Cytoplasmic and Glycolytic Pathway Proteins. In addition to specialised cell surface expressed plasminogen receptors, a number of proteins, usually considered to be restricted to the cytoplasm, have been found on the bacterial cell surface and are involved in interactions with plasminogen. Examples include the glycolytic pathway enzymes α-enolase and glyceraldehyde-3-phosphate dehydrogenase (GAPDH), DNaK, and elongation factor Tu (efTu) [30, 71, 79]. The mechanisms underlying the cell surface localisation of these proteins are not defined; however, their cell surface location has been confirmed in multiple species of bacteria [73, 82, 83, 85]. Unlike traditional cell wall anchored proteins, the contribution of glycolytic pathway enzymes to whole cell binding can typically only be shown indirectly, using blocking antibodies or competing concentrations of soluble recombinant proteins. This stems from the fact that these proteins are often metabolically essential for bacterial survival which prevents the construction of isogenic knockout mutant strains.

Interactions between the glycolytic pathway enzyme enolase and plasminogen have been characterised for several species of bacteria (Table 1). The most extensively studied of the bacterial enolases include those expressed by *S. pneumoniae* and *S. pyogenes.* Both have been shown to have a higher affinity for Lys-plasminogen than the circulating Glu-plasminogen or plasmin [90, 91].

Reports on the mechanism of plasminogen binding by bacterial enolases have been conflicting. *Pneumococcal* enolase contains an internal nonapeptide motif (FYDKERKVY), with the C-terminal lysine residues playing only a minor role in the interaction with plasminogen [65]. Like *S. pneumoniae,* several other bacterial enolases also appear to mediate plasminogen binding via internal lysine residues, including the enolase from *Bifidobacterium lactis,* for which internal residues Lys^{251} and Lys^{255}, as well as the negatively charged Glu^{252} are responsible for plasminogen binding [30]. However a recent study of the plasminogen-binding of oral *Streptococcal* enolase variants showed that plasminogen binding activity is conserved despite the loss of lysine residues within the internal nonapeptide, with the authors suggesting that the role of the first lysine in the internal nonapeptide in plasminogen binding may not be as critical as first thought [29]. For the *S. pyogenes* enolase (SEN), internal lysines Lys^{252} and Lys^{255} contribute significantly to plasminogen binding. However, the high affinity of SEN for plasminogen is also mediated in part by two lysine residues at the C-terminus (Lys^{434} and Lys^{435}) which are thought to stabilise the conformation of SEN's plasminogen binding site [68]. Site-directed mutagenesis of either the C-terminal or internal lysine motifs abrogate binding of plasminogen by SEN [69]. In contrast, the enolase of *S. mutans* does not have a functional internal plasminogen-binding site and may mediate plasminogen binding by C-terminal lysine residues only [74]. In all reported cases, bacterial plasminogen binding by enolase is inhibited by the lysine analogue EACA, indicating a role for the lysine binding sites within plasminogen in this interaction. However, it has yet to be established which LBS within plasminogen mediate interactions with enolase. It is possible that the different motifs responsible for plasminogen binding within diverse enolases interact with distinct LBS within plasminogen. One could hypothesise that C-terminal lysines interact with K1 of plasminogen, whilst internal lysines bind to K5, akin to the model proposed by Law et al. 2012 for the interaction of plasminogen and fibrin(ogen). Plasminogen binding is not conserved in all enolases, as evidenced by the finding that enolase from *Bacteroides fragilis* does not interact with plasminogen [92].

Similar to enolase, glyceraldehyde 3 phosphate dehydrogenase is a glycolytic pathway enzyme which has been shown to be located on the bacterial cell surface and to interact with plasminogen. GAPDH of *S. pyogenes* and *S. pneumoniae* binds preferentially to Lys-plasminogen and plasmin, and this interaction is mediated by the C-terminal lysine residue in GAPDH [93]. Interestingly, it has been shown that GAPDH of group B streptococcus interacts with both Glu-and Lys-plasminogen but not plasmin [94].

4.3. Indirect Plasminogen Binding. A number of bacterial pathogens possess the ability to interact with additional plasma proteins including IgG, α_2-macroglobulin, albumin, numerous complement factors, and fibrinogen [95]. These interactions are involved in pathogenic processes such as cell adherence and colonisation, evasion of the immune system and dissemination [95–97]. For *S. pyogenes*, the interaction of bacterial cell surface receptors with fibrinogen has been shown to play a role in the acquisition of cell surface plasmin activity.

Fibrinogen is a large, 340 kDa protein made up of two identical subunits connected by numerous disulphide linkages. Each subunit consists of three nonidentical polypeptide chains denoted Aα, Bβ, and γ [98]. These polypeptide chains are folded into a number of structural domains. The central E domain consists of the N-termini of all six polypeptide chains, the two D domains (one in each subunit) consist of C-terminal regions of Bβ and γ chains and a portion of the Aα chain, while the remaining portions of the two Aα chains form 2 αC domains [99]. Cleavage of fibrinogen by thrombin is the last step in the coagulation pathway and leads to the formation of fibrin. After thrombin cleavage, previously unexposed (cryptic) sites are revealed in fibrin molecules which initiate fibrin polymerisation and clot formation [100]. Polymerisation results in the exposure of additional cryptic-binding sites for a range of cell types, growth factors, and proteins including those involved in

fibrinolysis, such as tissue plasminogen activator, plasminogen, plasminogen activator inhibitor, and α_2-antiplasmin [101–103]. This diverse range of ligand interactions allows fibrin to participate in a variety of processes involved in tissue regeneration and also facilitates the tight regulation of haemostasis.

S. pyogenes secretes streptokinase, a plasminogen activating protein. Streptokinase binds to plasminogen SPD (Figure 1) and induces conformational changes in the latent active site of plasminogen producing an enzymatically active complex which, in addition to plasmin activity, also displays plasminogen activation activity [104]. While the main physiological role of plasmin is the degradation of fibrin, plasmin can also cleave a variety of other substrates including fibrinogen. Cleavage of soluble fibrinogen exposes cryptic sites within the molecule which allow it to interact with ligands that were previously nonreactive with the intact protein. Plasminogen-binding sites have been identified in D domain fibrinogen fragments [105] and the binding of plasminogen to this fragment enhances streptokinase-mediated plasminogen activation [106]. Additionally, fragment D is sufficient for interaction with fibrinogen receptors on the GAS cell surface [107, 108]. Therefore, at the site of infection, Plg-SK activator complexes can cleave fibrinogen, producing D domain fragments. These D domain fragments are then able to interact with both plasmin(ogen) (present in the activator complex and/or as free plasmin) and bacterial cell surface fibrinogen receptors thereby mediating the acquisition of unregulated plasmin activity onto the bacterial cell surface. This mechanism of plasmin acquisition appears to be important for those GAS strains that do not possess high-affinity plasminogen-binding proteins but do express fibrinogen-binding proteins such as PrtF1 and PrtF2 variants [109], M protein variants [110] and the lipoprotein Spy_0591 [111]. It is currently not known if a similar mechanism of plasmin acquisition involving fibrinogen fragments and bacterial fibrinogen receptors is functioning in other bacterial species.

4.4. Physiological Significance of Plasminogen Acquisition by Bacteria. The broad proteolytic activity of plasmin necessitates tight *in vivo* regulation. Within the host, this is achieved by specific mechanisms that control the generation of plasmin from plasminogen and by mechanisms that restrict plasmin activity to specific locations as required. The major circulating inhibitor of plasmin is α_2-antiplasmin. Lysine residues within α_2-antiplasmin stabilise binding to the kringles of plasmin(ogen), resulting in rapid inhibition of plasmin in solution. However, once bound to surfaces such as fibrin, or cell surface receptors, plasmin is partially protected from inactivation by α_2-antiplasmin [112–114]. Bacteria circumvent host regulatory mechanisms as cell surface bound plasminogen are more readily activated to plasmin, and, as in the host, this plasmin activity is not readily inhibited by host inhibitors [18, 19, 115]. Protection of plasmin from inhibition by binding to cell surface receptors appears to be central to the pathogenesis of several bacterial species and is utilised in a variety of pathogenic processes (summarised in Figure 2) [66, 73, 80, 116, 117].

Several bacterial species associated with highly invasive infections express receptors for plasminogen and plasmin, including *S. pyogenes*, *S. pneumoniae*, *S. aureus, P. aeruginosa, Y. pestis,* and *S. enteritidis*. Local thrombosis and microvascular occlusion during the early inflammatory response to bacterial infection can capture bacteria and prevent bacterial dissemination into deeper tissues. Surface-associated plasmin activity can facilitate fibrinolysis, preventing clot formation or promote the release of bacteria from a formed clot (Figure 2) [17, 107]. Furthermore, plasmin degradation of fibrinogen can initiate the release of products that affect blood vessel permeability and the accumulation of inflammatory cells [1, 118]. A major pathogenic consequence of bacterial plasminogen recruitment thus appears to be severe tissue destruction and overstimulation of the inflammatory response.

The direct degradation of ECM and basement membrane proteins and the activation of matrix metalloproteases by plasmin may enable bacteria to break down host tissue barriers (Figure 2). This is evidenced by the repeated demonstration that plasmin-coated bacteria are capable of penetrating ECM or basement membranes *in vitro* [119–121]. Plasminogen immobilised to the surface of *E. coli*, *H. pylori,* and *N. meningitidis* shows enhanced tPA-mediated plasminogen activation; whilst tPA- and uPA-activated plasmin at the surface of *S. typhimurium, B. burgdorferi*, *S. pneumoniae*, *S. agalactiae,* and *M. fermentans* facilitates the degradation of various ECM components, migration through endothelial and epithelial cell layers, or invasion of epithelial cells [18, 75, 122, 123]. The role of plasminogen acquisition in highly invasive infections is supported by a number of studies using animal models of infection, as well as several epidemiological studies. The ability to accumulate cell surface plasmin has been shown to be a prerequisite for systemic *S. pyogenes* infection in a humanised plasminogen mouse model [124–126]. Moreover, *B. burgdorferi* with active plasmin bound to their surface causes a more severe form of bacteraemia than their counterparts without active plasmin in a mouse model of spirochetemia [116]. Additionally, the abrogation of enolase-mediated plasminogen binding by *S. pneumoniae* significantly reduces the virulence of this pathogen in mice [65]. There are also epidemiological data to support the role of plasmin acquisition in bacterial pathogenesis. *E. coli* strains isolated from patients with colonic disease have been shown to bind significantly more plasminogen than *E. coli* isolates from healthy patients [127]. Similarly a study of *S. pyogenes* isolates from Northern Australia showed that isolates associated with invasive disease acquired significantly more cell surface plasminogen than noninvasive isolates [38]. However, oral streptococci display specific, high affinity plasminogen binding irrespective of their association with either benign dental plaque or severe inflammatory disease [128], and many commensal bacteria have been shown to recruit plasminogen to the bacterial cell surface (Table 1). This suggests that sequestration of plasminogen by bacteria may be important for bacterial survival in the host environment, with reports indicating a role for this interaction in both immune evasion and host colonisation [68, 129–131].

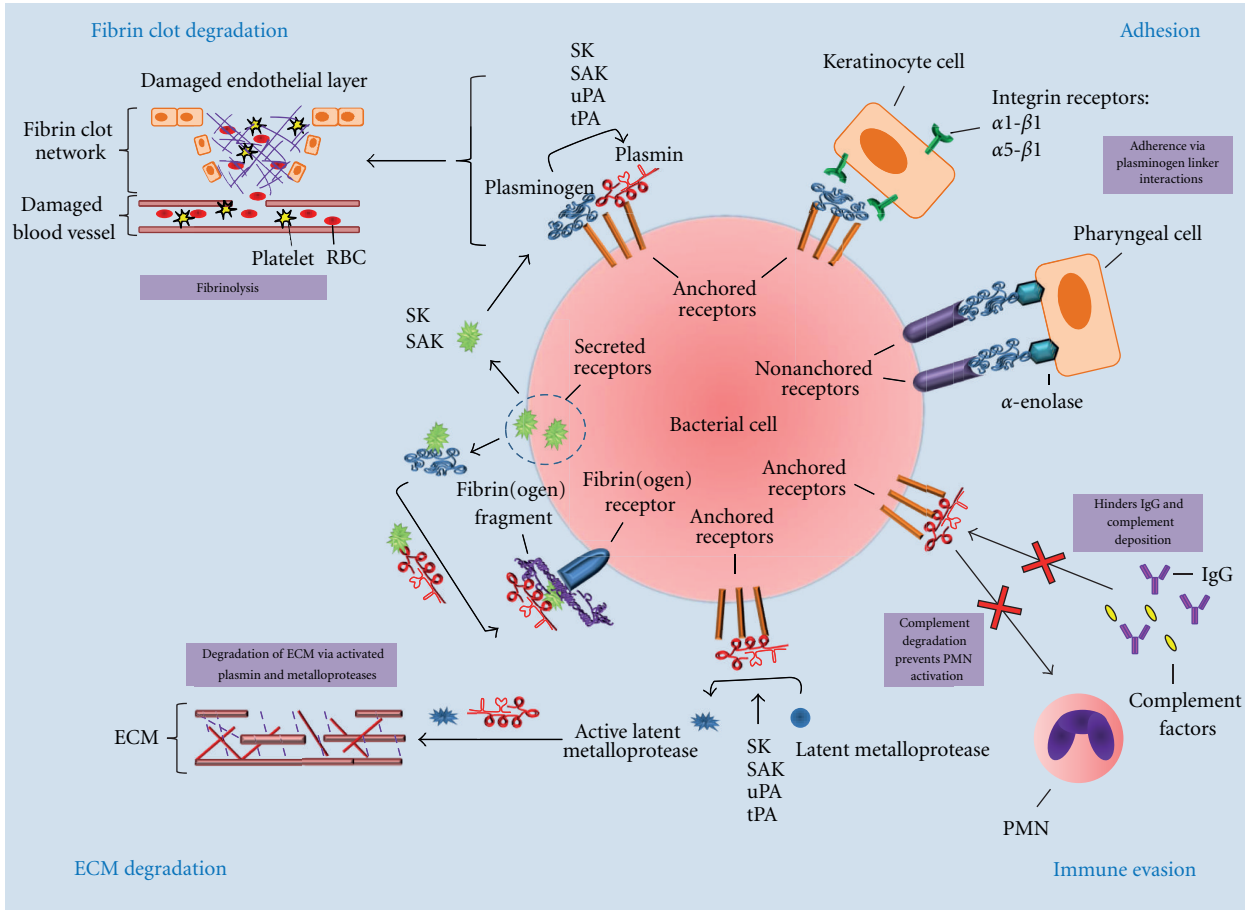

FIGURE 2: Mechanisms of bacterial cell surface plasmin(ogen) acquisition and its role in bacterial-host interactions. Plasmin(ogen) can be bound directly to the bacterial cell surface via cell-membrane-anchored receptors, nonanchored-cell-surface-associated receptors or indirectly through interactions with fibrinogen and cell surface fibrinogen receptors. Plasmin(ogen) localised on the bacterial cell surface is involved in four main processes; (1) ECM degradation via activated metalloproteases and plasmin; (2) fibrinolysis via plasmin; (3) immune evasion through plasmin-mediated degradation of immune effectors, including complement components and immunoglobulins; (4) adherence to host cells via plasminogen-linker interactions with host cell surface receptors. ECM: extracellular matrix; IgG: immunoglobulin G; RBC: red blood cell; SAK: staphylokinase; SEN: streptococcal α-enolase; Ska: streptokinase; tPA: tissue plasminogen activator; uPA; urokinase plasminogen activator.

Plasmin plays an integral role in the recruitment of host immune cells to sites of bacterial infection and is able to degrade essential components of the innate immune response such as the complement factors C3b, C4b, and C5 (Figure 2) [132–134]. Plasmin at the bacterial cell surface therefore provides organisms with the capacity to degrade immunoglobulins and complement proteins, thereby inhibiting the host immune response. Specifically, plasminogen activation by the bacterial activators staphylokinase (of *S. aureus*) and PgtE (of *S. typhimurium*) results in degradation of C3b, thereby preventing complement-driven phagocytosis. PgtE-generated plasmin has also been shown to degrade complement factors C4b and C5 [129, 133]. Similarly, uPA activated plasminogen at the surface of *L. interogans* and *B. anthracis* prevents deposition of IgG and C3b on the bacterial surface [135] and leads to a subsequent decrease in macrophage phagocytosis [71]. Furthermore, the ability of certain bacteria to activate plasminogen has been shown to alter the response of inflammatory cells to infection. The expression of the plasminogen activator Pla by *Yersinia pestis* appears to decrease the level of neutrophil infiltration in a mouse model of infection [136]. Clearly, there is a role for bacterial plasminogen acquisition in protecting bacteria from the host immune response. Whilst this has obvious significance for the initiation of systemic bacterial disease, it also has implications in host colonisation by commensal and pathogenic organisms alike.

A further role for plasminogen recruitment in bacterial colonisation has been demonstrated by several studies of plasminogen recruitment by streptococci. Plasminogen has been shown *in vitro* to act as a linker molecule between enolase at the surface of pharyngeal cells, and SEN at the surface of *S. pyogenes*, thus facilitating the adhesion process (Figure 2) [137]. When this bridging plasminogen molecule is activated by tPA to plasmin, it can digest intercellular junctions and disrupt cell monolayers in ECM models [137]. Similarly, the streptococcal M protein GSC3 has been shown to mediate plasminogen-dependant adherence

of streptococci to pharyngeal cells [40], implying a role for plasminogen binding in colonisation of the throat and oral cavity by bacteria. A role for plasminogen binding in colonisation has been further demonstrated for *S. pyogenes* interaction with keratinocytes. Plasminogen on the bacterial cell surface promoted the internalisation of streptococci by keratinocytes through the interaction with $\alpha 1\beta 1$- and $\alpha 5\beta 1$-integrins (Figure 2) [130]. In all the cases reported so far, the role of bacterially bound plasminogen in adherence/internalisation appears to function independently of the serine protease activity of plasmin.

5. Conclusions

The expression of receptors which enable localisation of plasminogen to the cell surface is a phenotype common to a multitude of bacteria. Since the initial identification of bacterial plasminogen receptors over 20 years ago, a myriad of receptor types have been identified, associated with both pathogenic and commensal bacterial species. The vast array of mechanisms via which different receptors interact with Glu-plasminogen, Lys-plasminogen, plasmin, and mini-plasmin suggests that these receptors may have evolved to mediate interactions with this abundant human protein under diverse physiological conditions. Indeed, recent studies show bacterial plasmin(ogen) acquisition is central to the onset of invasive pathogenesis via fibrin and ECM degradation; immune evasion via degradation of various immune effectors; and colonisation of the host (Figure 2). Much remains to be learned about how diverse plasminogen receptors interact with plasminogen. For many receptors, there is limited information on specificities of interaction with different forms of plasminogen and plasmin and on the location of binding within the plasminogen molecule. Recent structural studies suggest that the mechanism through which receptors interact with plasminogen can have different effects on the structure and activation of this protein which may ultimately influence the pathogenic process for many bacterial species [10]. Plasminogen receptors clearly play a central role in the relationship between bacteria and the host, and further elucidation of the nuances of how microbes interact with plasminogen will contribute significantly to our understanding of both the plasminogen molecule and bacterial pathogenesis in the future.

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