Author Manuscript
Author Manuscript
Author Manuscript
Author Manuscript

HHS Public Access
Author manuscript
*Biochem Soc Trans*. Author manuscript; available in PMC 2019 October 07.

Published in final edited form as:
*Biochem Soc Trans*. 2018 April 17; 46(2): 371–377. doi:10.1042/BST20170395.

# Glycobiology of syndecan-1 in bacterial infections

**Rafael S. Aquino**[1], **Yvonne Hui-Fang Teng**[1], **Pyong Woo Park**[1,2]

[1]Division of Respiratory Diseases, Boston Children's Hospital, Harvard Medical School, Boston, MA 02115, U.S.A.

[2]Division of Newborn Medicine, Boston Children's Hospital, Harvard Medical School, Boston, MA 02115, U.S.A.

## Abstract

Syndecan-1 (Sdc1) is a major cell surface heparan sulfate (HS) proteoglycan of epithelial cells, a cell type targeted by many bacterial pathogens early in their pathogenesis. Loss of Sdc1 in mice is a gain-of-function mutation that significantly decreases the susceptibility to several bacterial infections, suggesting that subversion of Sdc1 is an important virulence strategy. HS glycosaminoglycan (GAG) chains of cell surface Sdc1 promote bacterial pathogenesis by facilitating the attachment of bacteria to host cells. Engagement of cell surface Sdc1 HS chains by bacterial adhesins transmits signal through the highly conserved Sdc1 cytoplasmic domain, which can lead to uptake of intracellular bacterial pathogens. On the other hand, several bacteria that do not require Sdc1 for their attachment and invasion stimulate Sdc1 shedding and exploit the capacity of Sdc1 ectodomain HS GAGs to disarm innate defense mechanisms to evade immune clearance. Recent data suggest that select HS sulfate motifs, and not the overall charge of HS, are important in the inhibition of innate immune mechanisms. Here, we discuss several examples of Sdc1 subversion in bacterial infections.

## Primer on heparan sulfate proteoglycan and Sdc1 biology

Infectious diseases represent a major worldwide burden to human health, affecting individuals in both developed and developing countries. Mortality due to infections is extremely high in developing countries, especially in children where lower respiratory and gastrointestinal infections account for over 1.5 million deaths per year [1,2]. However, the number of deaths associated with infections is also unacceptably high in developed countries where mortality rates due to common infectious diseases, such as pneumonia, have remained essentially unchanged in the last several decades [3]. On top of that, the recent emergence of drug-resistant bacterial pathogens, shortage of new antimicrobial agents, and lower vaccination adherence rates add to the global public health concern of infectious diseases. These features indicate the importance and urgency for a better understanding of fundamental mechanisms underlying microbial pathogenesis to develop more effective prophylactic and therapeutic approaches.

**Correspondence:** Pyong Woo Park (pyong.park@childrens.harvard.edu).

Competing Interests
The Authors declare that there are no competing interests associated with the manuscript.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Bacteria are broadly classified by their structural characteristics (e.g. Gram-positive or -negative cell wall), cellular metabolism (e.g. aerobic vs. anaerobic), and morphology (e.g. cocci, bacilli, or spiro-chaetes). Bacterial pathogens can infect virtually all body sites, of which tissues that are directly connected to the outside world, such as the skin, respiratory tract, gastrointestinal tract, ocular surface, and urinary tract, are the most frequently infected. Most bacterial pathogens cause infections only when certain opportunities arise, such as when the immune system is compromised, when heavily contaminated water or food is consumed, or when physical barriers of the body are breached by injury due to trauma, burn, and invasive medical procedures, among others. Although innate and adaptive immune systems are capable of rapidly and efficiently eradicating infectious agents in most circumstances even when the barriers are breached, a large number of both Gram-positive and Gram-negative bacteria have either adapted or evolved versatile mechanisms to escape these host defense mechanisms.

Major bacterial pathogens elaborate virulence factors that enable them to exploit host components for their pathogenesis. Among these, HSPGs (heparan sulfate proteoglycans) are frequently targeted for the attachment, invasion, cell-cell transmission, dissemination, and evasion of host defense by many bacterial pathogens [4,5]. The ligand-binding activity of HSPGs is predominantly mediated by the HS GAG chain, which consists of unbranched, repeating disaccharide units of uronic acid, either glucuronic (GlcA) or iduronic (IdoA), alternating with an unsubstituted or *N*-substituted glucosamine on which the substituents are either acetate (GlcNAc, *N*-acetylglucosamine) or sulfate (GlcNS, *N*-sulfated glucosamine) (Figure 1) [4,5]. All HS *in vivo* is found covalently conjugated to specific core proteins as HSPGs [6,7]. In HSPG biosynthesis, a non-sulfated HS precursor consisting of repeating -GlcA-GlcNAc-disaccharide units is polymerized on the -GlcA-Gal-Gal-Xyl-tetrasaccharide link on specific Ser residues of HSPG core proteins. The heparan precursor is then extensively modified by *N*-deacetylase *N*-sulfotransferases (NDSTs), C5 epimerase, 2-*O*-sulfotransferase (2OST), 6OSTs, and 3OSTs in the Golgi [4,5]. The modification reactions largely proceed in a sequential manner but do not go to completion, resulting in highly structurally heterogeneous mature HS chains. The unique and complex structures of HS enable HSPGs to interact with many molecules and cells [8]. For example, *Chlamydia trachomatis* attachment is dependent on the degree of sulfation and not the total amount of HS [9], suggesting that specific HS sulfate motifs may be targeted during chlamydial infection. However, the significance and precise contribution of specific HS modifications in bacterial pathogenesis are largely unknown.

Sdc1 (CD138) is the founding member of the Sdc family of type I transmembrane HSPGs [10]. Sdc1 was first isolated from normal murine mammary gland epithelial cells [11] and rat livers [12], and was the first Sdc whose gene was cloned [13]. Starting at the *N*-terminus, Sdc1 core protein contains an extracellular domain that harbors both HS and chondroitin sulfate (CS) GAG chains, followed by highly conserved transmembrane and cytoplasmic domains (Figure 1A). The transmembrane domain contains the GxxxG dimerization motif found in all Sdcs and mediates both homotypic and heterotypic multimerization of Sdcs [14]. The cytoplasmic domain contains several conserved signaling and scaffolding motifs, including one invariant Ser, three invariant Tyr, and a Glu-Phe-Tyr-Ala PDZ-binding domain at the C-terminus [6,15]. Sdc1 is predominantly expressed on the surface of plasma cells and

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

epithelial cells. Sdc1 functions as a cell surface receptor for many, but not all, HS/heparin-binding molecules and cells. For example, while both Gram-positive *Staphylococcus aureus* [16] and Gram-negative *Pseudomonas aeruginosa* [17] can bind to HS, they do not bind to Sdc1 [18,19]. Furthermore, Sdc1 binds to several HS/heparin-binding extracellular matrix components, such as fibronectin, thrombospondin, tenascin, and types I, III, and V interstitial collagens, but not to type IV collagen, laminin, and vitronectin [6,20]. Sdcs can also function as soluble HSPG ectodomains when released from the cell surface by metalloproteinase (MP)-mediated ectodomain shedding, which apparently is an innate response to infection and inflammation [21]. Thus, Sdc1 regulates molecular and cellular interactions at both the cell surface and in the extracellular environment by regulating the activity, stability, oligomerization, conformation, or destination of both ligands and receptors. One of the major gaps in our understanding of Sdc1 biology centers on how it binds specifically to certain HS/heparin-binding molecules but not to others, and how these Sdc1 interactions modulate biological processes in health and disease, such as in infectious diseases.

## Functions of Sdc1 in bacterial infections

Sdc1 facilitates the attachment and internalization of many viruses, suggesting that it may function similarly in bacterial infections. Furthermore, Sdc1 is ubiquitously and abundantly expressed by epithelial cells, a cell type frequently targeted by many bacterial pathogens early in their pathogenesis. Indeed, several bacterial pathogens similarly bind to the HS moiety of cell surface Sdc1 to promote their attachment and internalization. *Listeria monocytogenes* is a Gram-positive, intracellular food-borne pathogen that crosses the intestinal mucosa and enters the systemic circulation where it can cause bacteremia and meningitis. *L. monocytogenes* expresses two major adhesins. Internalin A (InlA) binds to E-cadherin [22], whereas internalin B (InlB) binds to three receptors: the complement factor C1q receptor, the hepatocyte growth factor receptor Met, and cell surface HSPGs [23–26]. InlB promotes *L. monocytogenes* adhesion and internalization in epithelial cells, such as enterocytes and hepatocytes. Interestingly, binding of InlB to cell surface HSPGs is thought to facilitate *L. monocytogenes* internalization through Met by clustering both InlB and Met at the cell surface or by stabilizing the InlB-Met complex during bacterial uptake. While the role of Sdc1 in *L. monocytogenes* infection is not clearly established, overexpression of Sdc1 in ARH-77 myeloma cells increases susceptibility to *L. monocytogenes* infection [27], suggesting that Sdc1 may promote the adherence and invasion of *L. monocytogenes* in epithelial cells.

The Gram-negative bacterium *Neisseria gonorrhoeae* is the causative agent of sexually transmitted gonorrhea, which, along with chlamydial infection, is one of the two most common sexually transmitted bacterial diseases in the U.S.A. N. *gonorrhoeae,* via its cell surface OpaHSPG protein, binds to the HS chains of cell surface Sdc1 and Sdc4 [28,29]. Interestingly, although overexpression of full-length Sdc1 or Sdc4 constructs increases cellular infection in HeLa cells, mutant Sdc1 or Sdc4 lacking the cytoplasmic domain only supports gonococcal adhesion but not its internalization [29]. Furthermore, Sdc4 mutant constructs carrying lesions in the dimerization motif necessary for the binding of protein kinase C and phosphatidylinositol 4,5-bisphosphate, or lacking the invariant C-terminal Glu-

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Phe-Tyr-Ala PDZ-binding domain, do not support gonococcal invasion [29]. These data suggest that Sdc1 and Sdc4 not only promote *N. gonorrhoeae* attachment through their HS chains, but also facilitate gonococcal invasion through their cytoplasmic domain interactions (Figure 1B). How engagement of Sdc HS by gonococcal OpaHSPG leads to Sdc cytoplasmic domain-mediated signaling is unknown, but *N. gonorrhoeae* binding to cell surface HSPGs induces the generation of phosphatidylcholine-specific phospholipase C, diacylglycerol, acidic sphingomyelinase, and ceramide [30], suggesting that the cytoplasmic domain of Sdc1 may regulate pathways mediated by these signaling molecules. Moreover, the cytoplasmic domain of Sdc1 interacts with the cytoplasmic tail of β1 integrins and the small GTP-binding protein Rab5, and is thought to regulate the Rab5-dependent endocytosis of β1 integrins [31]. Because *N. gonorrhoeae* can also bind to fibronectin via OpaA and use fibronectin as a molecular bridge to stimulate its β1 integrin-mediated internalization [32], the cytoplasmic cross-talk between Sdc1, β1 integrins, and Rab5 may function as an on-off switch to regulate this invasion mechanism.

*Mycobacterium tuberculosis,* the causative agent of tuberculosis, continues to be a major global nemesis infecting an estimated one-third of the world's population and causing over 1.3 million deaths annually [33]. *M. tuberculosis* expresses a heparin-binding hemagglutinin adhesin (HBHA) that has been shown to function as an epithelial adhesin [34]. The HSPG receptor for HBHA has not been identified, but ablation of both Sdc1 and Sdc4 in mice leads to increased resistance to *M. tuberculosis* lung infection [35], suggesting that both Sdc1 and Sdc4 may serve as HBHA receptors. Overexpression of Sdc4 [35] or deletion of HBHA [36] increases and decreases *M. tuberculosis* attachment and invasion of type II alveolar epithelial cells *in vitro,* respectively. Moreover, HBHA ablation has no effect on the initial pulmonary colonization, but it significantly decreases the ability of *M. tuberculosis* to disseminate in mice [36]. This difference is not seen when wild-type and HBHA-deficient *M. tuberculosis* strains are injected intravenously into mice, suggesting that HBHA does not affect the ability of *M. tuberculosis* to colonize or replicate in distant organs. Altogether, these findings suggest that the interaction between HBHA and HS chains of Sdc1 and Sdc4 specifically mediates dissemination of primary pulmonary tuberculosis [36]. How this is accomplished is incompletely understood, but HBHA binding to epithelial HSPGs leads to reorganization of the actin cytoskeleton and triggers bacterial endocytosis [37]. Thus, similar to the role of Sdc1 in the pathogenesis of other intracellular bacterial pathogens, the HS chains are thought to mediate *M. tuberculosis* attachment, whereas the cytoplasmic domain is conjectured to regulate intracellular signaling events that lead to *M. tuberculosis* invasion.

In addition to facilitating bacterial attachment and invasion, Sdc1 has been shown to promote bacterial infections by inhibiting innate defense mechanisms as a shed ectodomain. *Sdc1−/−* mice show significantly decreased susceptibility to lung and burned skin infection by *P. aeruginosa* [18,38] and corneal infection by *S. aureus* [19,39] compared with wild-type (Wt) mice. However, several criteria indicate that the increased resistance of *Sdc1−/−* mice is not due to impaired bacterial attachment to host tissues due to the absence of cell surface Sdc1 [18,19]. Both *P. aeruginosa* and *S. aureus* do not bind to Sdc1, and Sdc1 does not promote the attachment of these bacteria to cultured epithelial cells. Furthermore, the bacterial tissue burden at early times post-infection is similar between Wt and *Sdc1−/−* mice, indicating that the initial attachment *in vivo* is not affected by the loss of Sdc1.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Instead, infection by both *P. aeruginosa* and *S. aureus* activates epithelial Sdc1 shedding in infected tissues, and administration of purified epithelial Sdc1 ectodomains or HS, but not CS or Sdc1 core protein, significantly enhances bacterial virulence in *Sdc1−/−* mice [18,19,40]. On the other hand, protamine, a clinical antidote for heparin, attenuates *P. aeruginosa* lung and burned skin infection [18,40]. Both *P. aeruginosa* and *S. aureus* induce Sdc1 shedding through specific virulence factors: LasA for *P. aeruginosa* [41] and α-toxin and β-toxin for *S. aureus* [42]. Interestingly, *Streptococcus pneumoniae* [43] and *Bacillus anthracis* [44] also stimulate Sdc1 shedding through specific virulence factors. *P. aeruginosa* LasA and *S. aureus* α- and β-toxins activate Sdc1 shedding by stimulating the host cell's shedding mechanism, whereas *S. pneumoniae* and *B. anthracis* directly shed Sdc1 ectodomains through their metalloproteinase virulence factors ZmpC and Npr599, respectively, suggesting that several bacterial pathogens may have evolved distinct mechanisms to provoke Sdc1 shedding for their pathogenesis (Figure 1C). Furthermore, *Sdc4−/−* mice are similarly susceptible to *S. aureus* corneal infection compared with Wt mice [39]. Taken together, these observations indicate that certain bacterial pathogens stimulate Sdc1 shedding to specifically exploit the activity of Sdc1 ectodomain HS to promote their infections.

The HS chains of Sdc1 ectodomains are thought to primarily enhance bacterial virulence through the inhibition of innate host defense. Neutrophil-mediated host defense, in particular, is inhibited by Sdc1 ectodomains during infection. Neutrophils are typically the first leukocytes to be recruited to the site of infection and are capable of eliminating pathogens by multiple mechanisms. Deficiencies in neutrophils, either inherited or acquired, often result in severe infections [45,46]. Ablation of Sdc1 enhances, whereas administration of purified Sdc1 ectodomains or HS inhibits neutrophil accumulation in a mouse model of endotoxic shock [47], suggesting that HS chains of Sdc1 ectodomains are negative regulators of neutrophil recruitment to infected tissues. How this is accomplished is incompletely understood, but Sdc1 ectodomain HS facilitates the removal of tissue-associated ELR+ CXC chemokines [47], which are a family of potent chemoattractants that induces neutrophil infiltration into infected or injured tissues.

Sdc1 ectodomains also bind to cationic antimicrobial peptides and inhibit their ability to kill bacterial pathogens in an HS-dependent manner [18,39]. Furthermore, in a mouse model of bacterial keratitis, the ability of purified Sdc1 ectodomains to promote *S. aureus* corneal infection is specifically dependent on 2-*O*-sulfate HS motifs [39]. Topical administration of purified Sdc1 ectodomain, HS, heparin, or engineered heparan compounds that contain 2-*O*-sulfate domains, such as *N*-or 6-*O*-desulfated heparin and chemoenzymatically *N*- and 2-*O*-sulfated heparosan, significantly increased the corneal *S. aureus* burden in mice. On the contrary, heparan compounds that do not contain 2-*O*-sulfate motifs, including 2-*O*-desulfated heparin, heparosan, and *N*-sulfated heparosan, did not. 2-*O*-sulfate HS motifs in Sdc1 ectodomains were determined to promote *S. aureus* corneal infection by interfering with neutrophil-mediated bacterial killing.

Interestingly, Sdc1 ectodomain and heparan compounds containing 2-*O*-sulfate motifs did not inhibit the intracellular phagocytic killing activity of neutrophils, but, instead, inhibited bacterial killing by antimicrobial factors secreted by activated neutrophils [39].

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Immunodepletion studies indicated that HS GAGs of Sdc1 ecto-domains specifically inhibit neutrophil-derived CRAMP (cathelin-related antimicrobial peptide), a cathelicidin antimicrobial peptide secreted by neutrophils and epithelial cells, and competition studies showed that 2-*O*-sulfated HS motifs mediate the ability of Sdc1 ectodomains to neutralize CRAMP (Figure 1D) [39]. These findings indicate that a specific subclass of sulfate groups, and not the overall charge of HS, permits Sdc1 ecto-domains to promote *S. aureus* corneal infection by inhibiting a key arm of neutrophil-mediated host defense. In addition, because neutrophils are essential in the eradication of most bacterial pathogens that cause acute infections, the ability of Sdc1 ectodomains to inhibit neutrophil recruitment and neutrophil-derived CRAMP may underlie how HS chains of Sdc1 ectodomains promote infection by bacteria that possess the ability to induce Sdc1 shedding.

## Concluding remarks

Ablation of Sdc1 is a gain-of-function mutation that increases the resistance of mice to several bacterial infections. On the other hand, Sdc1 ablation is a loss-of-function mutation in several sterile inflammatory diseases where mice become hypersusceptible to inflammatory tissue injury [10], suggesting that certain bacterial pathogens have either adapted or evolved ingenious virulence mechanisms to take advantage of essential Sdc1 activities to promote their infections. Sdc1 on the cell surface is exploited by several bacterial pathogens for their attachment and invasion of host cells, whereas Sdc1 ectodomains are used to disarm innate defense mechanisms. HS GAGs of Sdc1 mediate both of these pro-pathogenic activities. While studies on the critical structural features of Sdc1 HS are limited, studies that have investigated the role of HS modifications in microbial attachment, invasion, and immune evasion strongly suggest that certain HS motifs are more important than others [48]. *In vivo* infection studies using conditional knockout mice lacking HS biosynthetic and modification enzymes in specific cell types and cell-based infection assays using cells lacking or overexpressing specific HS structures should allow us to directly examine the biological significance and relevance of specific HS motifs in future studies. Moreover, bacterial pathogens may modulate HS structures by regulating the expression or activity of HS biosynthetic enzymes, or heparanase and sulfatases that can modify HS structures post-synthesis, and these potential virulence mechanisms also need to be explored. Furthermore, although bacterial pathogens studied thus far apparently target Sdc1 HS for their pathogenesis, the role of Sdc1 CS is clearly understudied and needs to be examined in more detail. Precise determination of essential Sdc1 GAG structures in bacterial pathogenesis should allow us to determine whether certain GAG motifs can serve as biomarkers and whether certain GAG structures can be targeted for novel therapeutic approaches against infectious diseases.

## Acknowledgments

Funding

P.W.P. is supported by National Institutes of Health grants R01 EY021765, R01 HL132573, and R21 AI126844.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

## Abbreviations

| | |
|---|---|
| **2OST** | 2-*O*-sulfotransferase |
| **3OST** | 3-*O*-sulfotransferase |
| **6OST** | 6-*O*-sulfotransferase |
| **CRAMP** | cathelin-related antimicrobial peptide |
| **CS** | chondroitin sulfate |
| **GAG** | glycosaminoglycan |
| **Gal** | galactose |
| **GlcA** | glucuronic acid |
| **GlcNAc** | *N*-acetylglucosamine |
| **GlcNS** | *N*-sulfated glucosamine |
| **HBHA** | heparin-binding hemagglutinin adhesin |
| **HS** | heparan sulfate |
| **HSPG** | heparan sulfate proteoglycan |
| **InlB** | internalin B |
| **MP** | metalloproteinase |
| **PTK** | protein tyrosine kinase |
| **Sdc** | syndecan |
| **Sdc1−/−** | syndecan-1 null |
| **Wt** | wild type |
| **Xyl** | xylose |

## References

1. Bygbjerg IC (2012) Double burden of noncommunicable and infectious diseases in developing countries. Science 337, 1499–1501 10.1126/science.1223466 [PubMed: 22997329]
2. Kyu HH, Pinho C, Wagner JA, Brown JC, Bertozzi-Villa A, Charlson FJ et al. (2016) Global and national burden of diseases and injuries among children and adolescents between 1990 and 2013: findings from the global burden of disease 2013 study. JAMA Pediatr. 170, 267–287 10.1001/jamapediatrics.2015.4276 [PubMed: 26810619]
3. Hansen V, Oren E, Dennis LK and Brown HE (2016) Infectious disease mortality trends in the United States, 1980–2014. JAMA 316, 2149–2151 10.1001/jama.2016.12423 [PubMed: 27893119]
4. Aquino RS and Park PW (2016) Glycosaminoglycans and infection. Front. Biosci 21, 1260–1277 10.2741/4455

Author Manuscript Author Manuscript Author Manuscript Author Manuscript


5. García B, Merayo-Lloves J, Martin C, Alcalde I, Quirós LM and Vazquez F (2016) Surface proteoglycans as mediators in bacterial pathogens infections. Front. Microbiol 7, 220 10.3389/fmicb.2016.00220 [PubMed: 26941735]
6. Bernfield M, Götte M, Park PW, Reizes O, Fitzgerald ML, Lincecum J et al. (1999) Functions of cell surface heparan sulfate proteoglycans. Annu. Rev. Biochem 68, 729–777 10.1146/annurev.biochem.68.1.729 [PubMed: 10872465]
7. Park PW, Reizes O and Bernfield M (2000) Cell surface heparan sulfate proteoglycans: selective regulators of ligand-receptor encounters. J. Biol. Chem 275, 29923–29926 10.1074/jbc.R000008200 [PubMed: 10931855]
8. Perrimon N and Bernfield M (2000) Specificities of heparan sulphate proteoglycans in developmental processes. Nature 404, 725–728 10.1038/35008000 [PubMed: 10783877]
9. Rosmarin DM, Carette JE, Olive AJ, Starnbach MN, Brummelkamp TR and Ploegh HL (2012) Attachment of *Chlamydia trachomatis* L2 to host cells requires sulfation. Proc. Natl Acad. Sci. U.S.A 109, 10059–10064 10.1073/pnas.1120244109 [PubMed: 22675117]
10. Teng Y-H, Aquino RS and Park PW (2012) Molecular functions of syndecan-1 in disease. Matrix Biol. 31, 3–16 10.1016/j.matbio.2011.10.001 [PubMed: 22033227]
11. Rapraeger AC and Bernfield M (1983) Heparan sulfate proteoglycans from mouse mammary epithelial cells. A putative membrane proteoglycan associates quantitatively with lipid vesicles. J. Biol. Chem 258, 3632–3636 [PubMed: 6219993]
12. Kjellen L, Pettersson I and Hook M (1981) Cell-surface heparan sulfate: an intercalated membrane proteoglycan. Proc. Natl Acad. Sci. U.S.A 78, 5371–5375 10.1073/pnas.78.9.5371 [PubMed: 6458040]
13. Saunders S, Jalkanen M, O'Farrell S and Bernfield M (1989) Molecular cloning of syndecan, an integral membrane proteoglycan. J. Cell Biol 108, 1547–1556 10.1083/jcb.108.4.1547 [PubMed: 2494194]
14. Dews IC and Mackenzie KR (2007) Transmembrane domains of the syndecan family of growth factor coreceptors display a hierarchy of homotypic and heterotypic interactions. Proc. Natl Acad. Sci. U.S.A 104, 20782–20787 10.1073/pnas.0708909105 [PubMed: 18093920]
15. Lambaerts K, Wilcox-Adelman SA and Zimmermann P (2009) The signaling mechanisms of syndecan heparan sulfate proteoglycans. Curr. Opin. Cell Biol 21, 662–669 10.1016/j.ceb.2009.05.002 [PubMed: 19535238]
16. Liang OD, Ascencio F, Fransson L and Wadström T (1992) Binding of heparan sulfate to *Staphylococcus aureus*. Infect. Immun 60, 899–906 [PubMed: 1541563]
17. Bucior I, Pielage JF and Engel JN (2012) *Pseudomonas aeruginosa* pili and flagella mediate distinct binding and signaling events at the apical and basolateral surface of airway epithelium. PLoS Pathog. 8, e1002616 10.1371/journal.ppat.1002616 [PubMed: 22496644]
18. Park PW, Pier GB, Hinkes MT and Bernfield M (2001) Exploitation of syndecan-1 shedding by *Pseudomonas aeruginosa* enhances virulence. Nature 411, 98–102 10.1038/35075100 [PubMed: 11333985]
19. Hayashida A, Amano S and Park PW (2011) Syndecan-1 promotes *Staphylococcus aureus* corneal infection by counteracting neutrophil-mediated host defense. J. Biol. Chem 285, 3288–3297 10.1074/jbc.M110.185165
20. Bernfield M, Kokenyesi R, Kato M, Hinkes MT, Spring J, Gallo RL et al. (1992) Biology of the syndecans: a family of transmembrane heparan sulfate proteoglycans. Annu. Rev. Cell Biol 8, 365–393 10.1146/annurev.cb.08.110192.002053 [PubMed: 1335744]
21. Hayashida K, Bartlett AH, Chen Y and Park PW (2010) Molecular and cellular mechanisms of ectodomain shedding. Anat. Rec 293, 925–937 10.1002/ar.20757
22. Mengaud J, Ohayon H, Gounon P, Mège R-M and Cossart P (1996) E-cadherin is the receptor for internalin, a surface protein required for entry of *L. monocytogenes* into epithelial cells. Cell84, 923–932 10.1016/S0092-8674(00)81070-3 [PubMed: 8601315]
23. Braun L, Ghebrehiwet B and Cossart P (2000) gC1q-R/p32, a C1q-binding protein, is a receptor for the InlB invasion protein of *Listeria monocytogenes*. EMBO J. 19, 1458–1466 10.1093/emboj/197.1458 [PubMed: 10747014]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript


24. Veiga E and Cossart P (2005) Listeria hijacks the clathrin-dependent endocytic machinery to invade mammalian cells. Nat. Cell Biol 7, 894–900 10.1038/ncb1292 [PubMed: 16113677]
25. Jonquieres R, Pizarro-Cerda J and Cossart P (2001) Synergy between the N- and C-terminal domains of InlB for efficient invasion of non-phagocytic cells by *Listeria monocytogenes*. Mol. Microbiol 42, 955–965 10.1046/j.1365-2958.2001.02704.x [PubMed: 11737639]
26. Banerjee M, Copp J, Vuga D, Marino M, Chapman T, van der Geer P et al. (2004) GW domains of the *Listeria monocytogenes* invasion protein InlB are required for potentiation of Met activation. Mol. Microbiol 52, 257–271 10.1111/j.1365-2958.2003.03968.x [PubMed: 15049825]
27. Henry-Stanley MJ, Hess DJ, Erickson EA, Garni RM and Wells CL (2003) Role of heparan sulfate in interactions of *Listeria monocytogenes* with enterocytes. Med. Microbiol. Immunol 192, 107–115 10.1007/s00430-002-0165-7 [PubMed: 12684756]
28. van Putten JP and Paul SM (1995) Binding of syndecan-like cell surface proteoglycan receptors is required for *Neisseria gonorrheae* entry into human mucosal cells. EMBO J. 14, 2144–2154 [PubMed: 7774572]
29. Freissler E, Meyer auf der Heyde A, David G, Meyer TF and Dehio C (2000) Syndecan-1 and syndecan-4 can mediate the invasion of $Opa_{HSPG}$-expressing *Neisseria gonorrhoeae* into epithelial cells. Cell. Microbiol 2, 69–82 10.1046/j.1462-5822.2000.00036.x [PubMed: 11207564]
30. Grassmé H, Gulbins E, Brenner B, Ferlinz K, Sandhoff K, Harzer K et al. (1997) Acidic sphingomyelinase mediates entry of *N. gonorrhoeae* into nonphagocytic cells. Cell91, 605–615 10.1016/S0092-8674(00)80448-1 [PubMed: 9393854]
31. Hayashida K, Stahl PD and Park PW (2008) Syndecan-1 ectodomain shedding is regulated by the small GTPase Rab5. J. Biol. Chem 283, 35435–35444 10.1074/jbc.M804172200 [PubMed: 18957427]
32. van Putten JPM, Duensing TD and Cole RL (1998) Entry of OpaA+ gonococci into HEp-2 cells requires concerted action of glycosaminoglycans, fibronectin and integrin receptors. Mol. Microbiol 29, 369–379 10.1046/j.1365-2958.1998.00951.x [PubMed: 9701828]
33. Zumla A, Raviglione M, Hafner R and von Reyn CF (2013) Tuberculosis. N. Engl. J. Med 368, 745–755 10.1056/NEJMra1200894 [PubMed: 23425167]
34. Menozzi FD, Bischoff R, Fort E, Brennan MJ and Locht C (1998) Molecular characterization of the mycobacterial heparin-binding hemagglutinin, a mycobacterial adhesin. Proc. Natl Acad. Sci. U.S.A 95, 12625–12630 10.1073/pnas.95.21.12625 [PubMed: 9770536]
35. Zimmermann N, Saiga H, Houthuys E, Moura-Alves P, Koehler A, Bandermann S et al. (2016) Syndecans promote mycobacterial internalization by lung epithelial cells. Cell. Microbiol 18, 1846–1856 10.1111/cmi.12627 [PubMed: 27279134]
36. Pethe K, Alonso S, Biet F, Delogu G, Brennan MJ, Locht C et al. (2001) The heparin-binding haemagglutinin of *M. tuberculosis* is required for extrapulmonary dissemination. Nature 412, 190–194 10.1038/35084083 [PubMed: 11449276]
37. Menozzi FD, Reddy VM, Cayet D, Raze D, Debrie A-S, Dehouck M-P et al. (2006) *Mycobacterium tuberculosis* heparin-binding haemagglutinin adhesin (HBHA) triggers receptor-mediated transcytosis without altering the integrity of tight junctions. Microbes Infect. 8, 1–9 10.1016/j.micinf.2005.03.023 [PubMed: 15914062]
38. Haynes A III, Ruda F, Oliver J, Hamood AN, Griswold JA, Park PW et al. (2005) Syndecan 1 shedding contributes to *Pseudomonas aeruginosa* sepsis. Infect. Immun 73, 7914–7921 10.1128/IAI.73.12.7914-7921.2005 [PubMed: 16299282]
39. Hayashida A, Amano S, Gallo RL, Linhardt RJ, Liu J and Park PW (2015) 2-*O*-Sulfated domains in syndecan-1 heparan sulfate inhibit neutrophil cathelicidin and promote *Staphylococcus aureus* corneal infection. J. Biol. Chem 290, 16157–16167 10.1074/jbc.M115.660852 [PubMed: 25931123]
40. Haynes A III, Rumbaugh KP, Park PW, Hamood AN and Griswold JA (2005) Protamine sulfate reduces the susceptibility of thermally injured mice to *Pseudomonas aeruginosa* infection. J. Surg. Res 123, 109–117 10.1016/j.jss.2004.07.251 [PubMed: 15652958]
41. Park PW, Pier GB, Preston MJ, Goldberger O, Fitzgerald ML and Bernfield M (2000) Syndecan-1 shedding is enhanced by LasA, a secreted virulence factor of *Pseudomonas aeruginosa*. J. Biol. Chem 275, 3057–3064 10.1074/jbc.275.5.3057 [PubMed: 10652286]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

42. Park PW, Foster TJ, Nishi E, Duncan SJ, Klagsbrun M and Chen Y (2004) Activation of syndecan-1 ectodomain shedding by *Staphylococcus aureus* α-toxin and β-toxin. J. Biol. Chem 279, 251–258 10.1074/jbc.M308537200 [PubMed: 14573623]

43. Chen Y, Hayashida A, Bennett AE, Hollingshead SK and Park PW (2007) *Streptococcus pneumoniae* sheds syndecan-1 ectodomains through ZmpC, a metalloproteinase virulence factor. J. Biol. Chem 282, 159–167 10.1074/jbc.M608542200 [PubMed: 17098735]

44. Chung M-C, Popova TG, Millis BA, Mukherjee DV, Zhou W, Liotta LA et al. (2006) Secreted neutral metalloproteases of *Bacllus anthracis* as candidate pathogenic factors. J. Biol. Chem 281, 31408–31418 10.1074/jbc.M605526200 [PubMed: 16926147]

45. Klein C (2011) Genetic defects in severe congenital neutropenia: emerging insights into life and death of human neutrophil granulocytes. Annu. Rev. Immunol 29, 399–413 10.1146/annurev-immunol-030409-101259 [PubMed: 21219176]

46. Bardoel BW, Kenny EF, Sollberger G and Zychlinsky A (2014) The balancing act of neutrophils. Cell Host Microbe 15, 526–536 10.1016/j.chom.2014.04.011 [PubMed: 24832448]

47. Hayashida K, Parks WC and Park PW (2009) Syndecan-1 shedding facilitates the resolution of neutrophilic inflammation by removing sequestered CXC chemokines. Blood 114, 3033–3043 10.1182/blood-2009-02-204966 [PubMed: 19638625]

48. García B, Merayo-Lloves J, Rodríguez D, Alcalde I, García-Suárez O, Alfonso JF et al. (2016) Different use of cell surface glycosaminoglycans as adherence receptors to corneal cells by gram positive and gram negative pathogens. Front. Cell. Infect. Microbiol 6, 173 10.3389/fcimb.2016.00173 [PubMed: 27965938]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

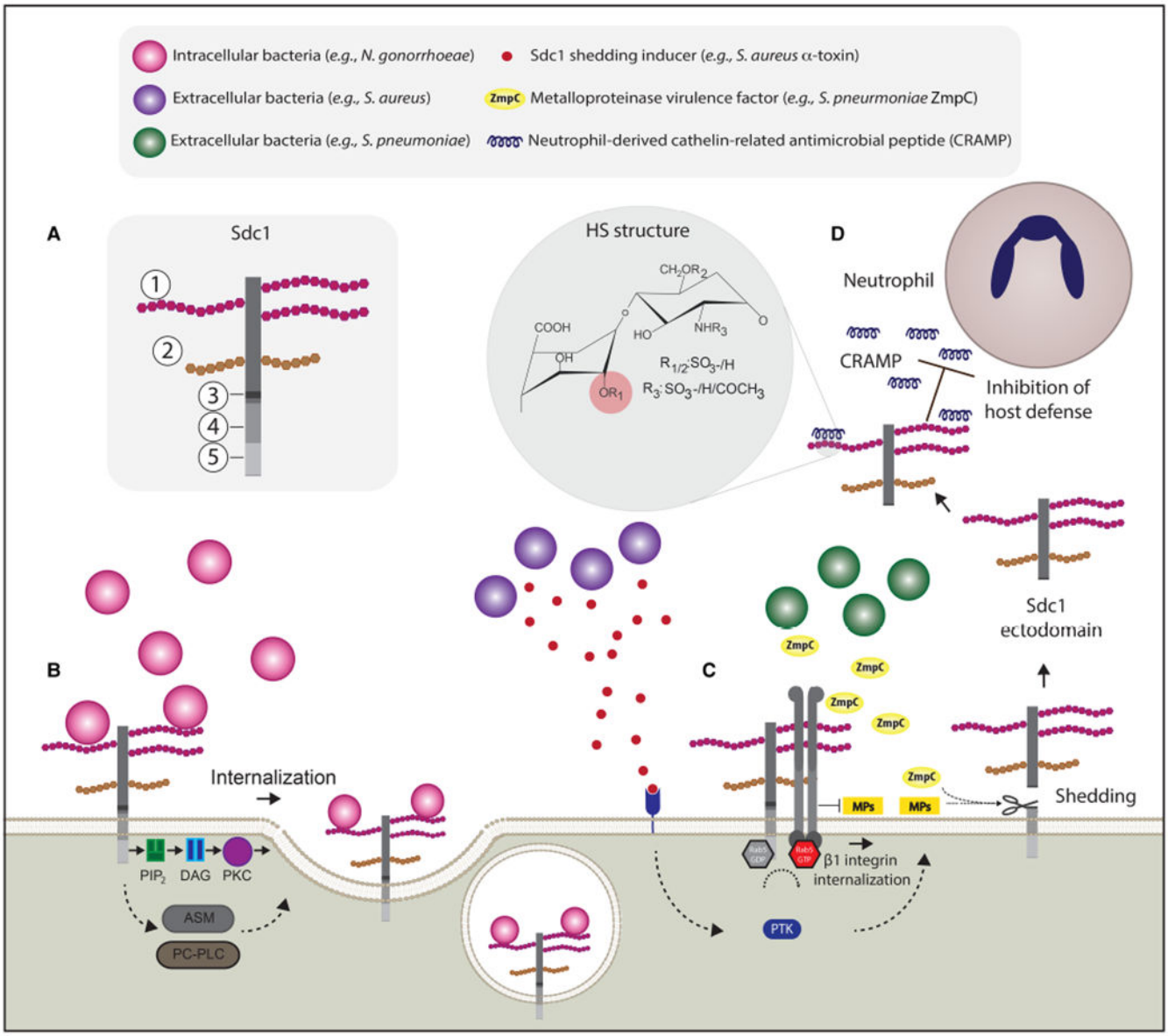


**Figure 1. Mechanisms of subversion of Sdc1 by bacterial pathogens.**

(**A**) Sdc1 structure: Sdc1 core protein is a type I transmembrane protein that contains an extracellular domain that harbors both (1) HS and (2) CS chains, (3) a juxtamembrane region that is cleaved by MPs during shedding, and highly conserved (4) transmembrane and (5) cytoplasmic domains. The disaccharide structure of HS is shown. (**B**) Sdc1 as an adhesion and internalization receptor: attachment of bacterial pathogens (e.g. *N. gonorrhoeae)* to cell surface Sdc1 triggers intracellular signaling that leads to bacterial internalization. (**C**) Sdc1 shedding: bacterial pathogens secrete virulence factors that can enhance Sdc1 shedding by activating the host cell's MP-mediated shedding mechanism that is regulated by PTKs, Rab5, and β1 integrins (e.g. *S. aureus* α-toxin) or by directly cleaving Sdc1 ectodomains (e.g. *S. pneumoniae* ZmpC). (**D**) Sdc1 inhibition of innate host defense:

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Sdc1 ectodomains bind to and neutralize the antibacterial activity of cationic antimicrobial peptides (e.g. neutrophil-derived CRAMP).