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Review

The MSCRAMM Family of Cell-Wall-Anchored Surface Proteins of Gram-Positive Cocci

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The microbial surface components recognizing adhesive matrix molecules (MSCRAMMs) are a family of proteins that are defined by the presence of two adjacent IgG-like folded subdomains. These promote binding to ligands by mechanisms that involve major conformational changes exemplified by the binding to fibrinogen by the 'dock-lock-latch' mechanism or to collagen by the 'collagen hug'. Clumping factors A and B are two such MSCRAMMs that have several important roles in the pathogenesis of *Staphylococcus aureus* infections. MSCRAMM architecture, ligand binding, and roles in infection and colonization are examined with a focus on recent developments with clumping factors.

Highlights

Shear stress mechanical forces trigger interactions between MSCRAMMs and their ligands.

MSCRAMMs bound to ligands via the dock-lock-latch or collagen-hug mechanisms can only be separated by very strong forces.

Clumping factor A has a crucial role in attachment to the endothelium during endovascular infections.

Clumping factor B binding to loricrin is important in early abscess formation as well as in adhesion to corneocytes.

MSCRAMMs also bind a plethora of ligands by mechanisms that do not involve dock-lock-latch.

Cell-Wall-Anchored Proteins of Gram-Positive Cocci

Pathogenic Gram-positive cocci express a plethora of virulence factors, including surface proteins that are covalently anchored to cell wall peptidoglycan and which are important for the bacteria to colonize the host and to promote infections [1].

Cell-wall-anchored (CWA) proteins can be classified based on structural and functional properties [1,2]. The most prevalent are the MSCRAMMs which are defined by the presence of two tandemly arrayed IgG-like folded domains that are involved in ligand binding (Figure 1).

There are two families of MSCRAMMs, those that are related to clumping factor A (ClfA) of *Staphylococcus aureus* and SdrG of *Staphylococcus epidermidis* (the Clf-Sdr-FnBP family), and those that are similar to the collagen-binding protein of *S. aureus* (the Cna family) (Table 1). They bind ligands by mechanisms that involve large conformational changes exemplified by ClfA and SdrG binding to fibrinogen by dock-lock-latch (DLL) and Cna binding collagen by the collagen hug (CH).

A single MSCRAMM can often perform several functions. Since the repertoire of surface proteins is limited, individual proteins have been subjected to selective pressure to carry out different functions associated with colonization of host tissues and evasion of host defenses. Several Clf-like MSCRAMMs have multiple ligands and bind some of them by mechanisms that do not involve DLL (Table 2).

This review summarizes the current understanding of the structure and functions of MSCRAMMs and shows how they promote adhesion to the extracellular matrix and to host cells. Particular emphasis is placed on recent advances in understanding the mechanistic basis of ligand binding, including the role of shear stress in strengthening interactions and newly discovered roles for Clf proteins in promoting colonization and infection.

MSCRAMM Architecture

Linkage to the Cell Wall

The typical MSCRAMM is a multidomain protein that is anchored to cell wall peptidoglycan by sortase A following secretion via the Sec apparatus and removal of the secretory signal sequence (Figure 1) [1,3]. The ligand binding A domain is located at the N terminus. The C terminal cell wall sorting domain comprises an LPXTG motif followed by a hydrophobic membrane-spanning domain and positively charged residues at the extreme C terminus. Sortase A catalyzes the cleavage of the LPXTG motif followed by covalent coupling of the secreted protein to the peptidoglycan precursor lipid II [3]. The transglycosylase activity of PBP2 catalyzes transfer of the CWA protein-modified peptidoglycan

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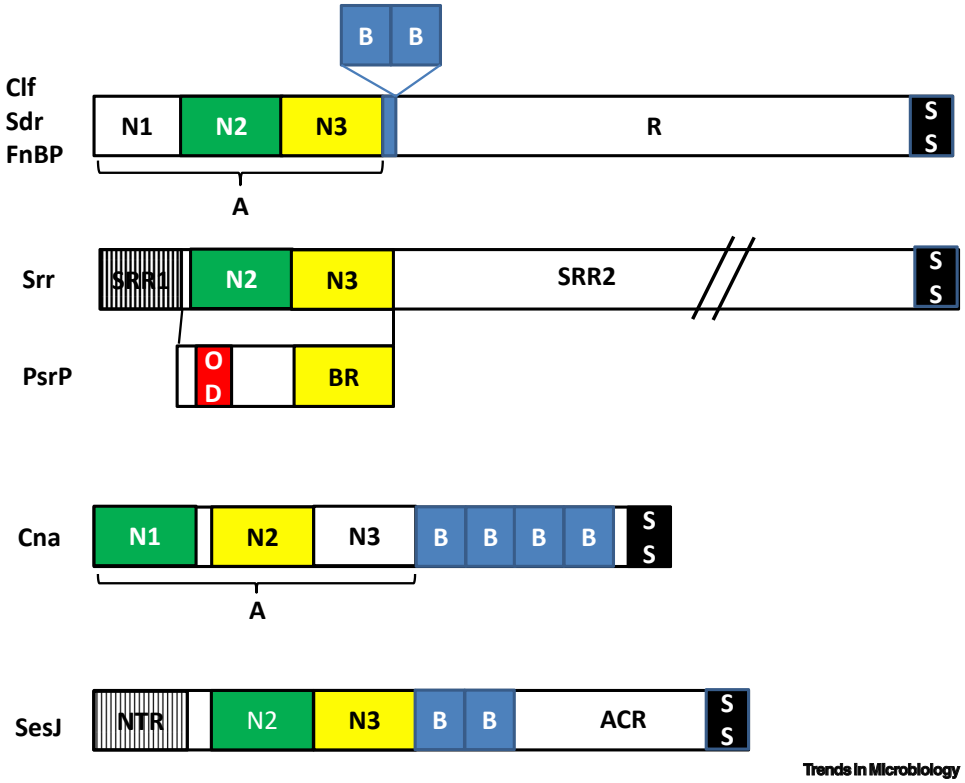

Figure 1. Domain Organization of Microbial Surface Components Recognizing Adhesive Matrix Molecules (MSCRAMMs).

The archetypal MSCRAMM families Clf-Sdr-FnBP and Cna have A domains at their N termini with N2-N3 or N1-N2 comprising the minimum ligand-binding subdomains. The Sdr proteins have two to five B repeats located between the A domain and the extended unfolded repeat region R. Region R is composed of variable numbers of serine–aspartate dipeptide repeats (Clf, Sdr) or 10/11 ~39-residue fibronectin-binding repeats (FnBPs). MSCRAMM proproteins have an N terminal secretory signal sequence (not shown) and a C terminal sorting signal (SS) for anchorage to peptidoglycan. The Cna family has variable numbers of B repeats and lacks flexible stalks. The Srr proteins have two serine-rich repeat (Srr) domains flanking the ligand-binding domain which comprises N2 and N3 homologs that participate in Fg binding by dock-lock-latch (DLL) or a single IgG-like folded binding region (BR) adjacent to an oligomerization domain (OD). Srr proteins have very long C terminal SRR2 domains. The SesJ family of proteins are composites with typical MSCRAMM ligand-binding regions (N2, N3, ligands not known) flanked by B repeats similar to those in the Sdr family, N terminal repeats (NTRs) and aspartate-containing repeats (ACRs) close to the C terminus. The figures are not drawn to scale.

subunit into the growing peptidoglycan polymer. The protein is thus tethered to the cell wall, and the N terminal ligand binding A domain is projected away from the surface (Figure 2).

The MSCRAMM Family

The MSCRAMMs are defined by the presence of two adjacent separately folded subdomains in the N terminal A region that comprises structures called IgG-like folds (Figure 1) [1]. The A domains of the Clf-Sdr group have three separately folded subdomains of which N2 and N3 comprise IgG-like folds which bind ligand by the DLL mechanism (see below).

The A domains are separated from the cell wall anchoring region by unstructured repeats that form flexible stalks. These are the serine aspartate dipeptide repeats of the Clf-Sdr proteins or ~29 residue fibronectin-binding repeats of the related fibronectin-binding proteins (FnBPs), an extensive serine-

MSCRAMM	Host	Ligand	Refs
ClfA	*Staphylococcus aureus*	Fibrinogen. 17-residue γ-chain C terminal peptide, residues 395–411	[21]
		Second binding site on γ-globular domain of the D region	[22]
ClfB	*S. aureus*	Fibrinogen Aα-chain αC region repeat five residues 316–328	[20,60]
		Cytokeratin 10 C terminal 'tail' region comprising six quasi-repeats of Tyr-(Gly-Ser)$_n$ omega Ω loops	[61]
		Loricrin Ω loops. Multiple binding sites. Highest affinity site in region 2 (residues 152–230)	[53]
		Cytokeratin 8 C terminal 'tail' region single Ω loop	[62]
SdrE	*S. aureus*	Complement factor H. Residues 1206–1226 at the C terminus of the distal complement control protein unit 20	[23]
Bbp	*S. aureus*	Fibrinogen Aα chain residues 561–575 overlapping integrin $\alpha_V b_3$ and $\alpha_5\beta_1$ RGDS binding site	[63]
FnBPA	*S. aureus*	Fibrinogen γ-chain. 17-residue γ-chain C terminal peptide, residues 395–411	[64]
		Elastin[b]	[65]
FnBPB	*S. aureus*	Fibrinogen γ-chain. 17-residue γ-chain C terminal peptide, residues 395–411	[66]
		Histone H3	[41]
		Elastin[b]	[65]
Fbl	*Staphylococcus lugdunensis*	Fibrinogen γ-chain. 17-residue γ-chain C terminal peptide, residues 395–411	[67]
SdrG	*Staphylococcus epidermidis*	Fibrinogen B β-chain N terminal residues 6–20 overlapping thrombin cleavage sites	[14]
SpsD	*Staphylococcus pseudintermedius*	Human fibrinogen γ-chain. 17-residue γ-chain C terminal peptide, residues 395–411 Elastin[b] (most closely related to FnBPB)	[68]
SpsL	*S. pseudintermedius*	High affinity binding site in the polymorphic region of the α-chain of canine fibrinogen	[69,102]
Srr1 Srr2	*Streptococcus agalactiae*	Fibrinogen Aα chain repeats 6–8 residues 329–367	[70]
Cna	*S. aureus*	Collagen type I. Collagen hug	[24,25,71]
		Complement factor C1q and laminin. Docking without completed hug	[26,71]
Ace	*Enterococcus faecalis*	Collagen	[72]

Table 1. MSCRAMM Ligands That Bind by Dock-Lock-Latch (DLL) or Collagen Hug (CH)[a]

[a]The DLL or CH mechanism was proven by X-ray crystallography of the MSCRAMM in complex with the ligand and/or was inferred from analysis of recombinant proteins with amino acid substitutions in the ligand-binding trench or lacking the latching peptide. In the case of Bbp, neither of these tests was met but the biophysical analysis of the MSCRAMM–ligand peptide interaction was sufficiently robust to infer that DLL was involved. Similarly, for ClfB binding to cytokeratin 8 and localization of binding site in an omega loop, the *in vitro* analysis is consistent with DLL.

[b]Elastin binding to FnBPs and SpsD was inferred by showing reduced binding by recombinant proteins with substitutions in the ligand-binding trench and the lock-latch region that abrogated fibrinogen binding.

rich repeat region (Srr) in the Srr proteins, and the aspartate-containing serine-rich (ACR) repeats of the SesJ family [4–6].

Some proteins in the ClfA-Sdr group, namely SdrC, SdrD, and SdrE of *S. aureus* and SdrF of *S. epidermidis*, as well as the SesJ family, have between two and five 110–113 residue B repeats. These are separately folded and act to project the A domain away from the cell surface [7]. Their structural integrity is dependent of several Ca^{2+} ions, one of which binds to a site that resembles the EF hand structure in eukaryotic Ca^{2+}-binding proteins [7,8]. The B1 repeat of SdrD interacts with residues in the A domain and may influence ligand binding [8]. The B repeats of SdrF bind weakly to collagen, and it is possible that other B repeats also have ligand-binding activity [9].

MSCRAMM	Host	Ligands	Binding	Refs
ClfA	*Staphylococcus aureus*	Complement factor I	Captured from serum. Mechanism unknown	[73,74]
		von Willebrand factor binding protein	High-affinity binding measured by surface plasmon resonance	[48]
		Annexin 2	Pull down assays. *In vitro* protein–protein interactions	[75]
SdrC	*S. aureus*	β-neurexin	Biophysical studies	[76]
		SdrC homophilic interactions	Biofilm formation AFM	[27,31]
		Adhesion to hydrophobic surfaces		[31]
SdrD	*S. aureus*	Desmoglein-1	Bacterial adhesion to ligand. *In vitro* protein–protein interaction. Affinity not measured	[77]
		Unknown ligand	X-ray structure of apo form including B domain	[8]
Bbp	*S. aureus*	Bone sialoprotein	Recombinant protein-binding assays	[78]
FnBPA	*S. aureus*	Plasminogen	Binding assays with purified proteins and bacterial mutants. AFM	[36,37]
		FnBPA homophilic interactions	Biofilm formation. Binding assays with purified proteins and bacterial mutants. AFM	[28,30]
FnBPB	*S. aureus*	Plasminogen	Binding assays with purified proteins and bacterial mutants. AFM	[36,37]
		FnBPB homophilic interactions	Biofilm formation. Binding assays with purified proteins and bacterial mutants. AFM	[30]
		Fibronectin	Binding assays with purified proteins	[66]
SdrG	*Staphylococcus epidermidis*	$\alpha_V\beta_3$ integrin	Bacterial adhesion assays. Mechanism not investigated	[79]
SdrF	*S. epidermidis*	Collagen type I. Cytokeratin 1 and 10	Bacterial adhesion assays. Binding assays with purified proteins. AFM	[9,80,81]
SpsD	*Staphylococcus pseudintermedius*	Fibronectin, cytokeratin 10	Binding assays with purified proteins. Not DLL	[68]
		Canine corneocytes		[82]
SpsO	*S. pseudintermedius*	Canine corneocytes	Bacterial adhesion assays. Ligand not known	[82]
SdrI	*Staphylococcus saprophyticus*	Fibronectin. Collagen	Recombinant protein solid phase binding. Bacterial adhesion assays	[83,84]
PsrP	*Streptococcus pneumoniae*	Keratin 10 C terminal helical tail-rod domain	Single DEV-IgG fold domain. X-ray structure and modeling. *In vitro* binding and bacterial adhesion	[13]
		Homophilic interactions	Biofilm	[85]
GspB	*Streptococcus gordonii*	Sialyl T antigen glycoprotein	Single DEV-IgG folded domain structurally similar to PsrP. Bacterial adhesion assays and protein-binding assays	[86]
Fap1	*Streptococcus parasanguis*	Host glycoproteins	Single DEV-IgG folded domain structurally similar to PsrP	[87]

Table 2. Ligands That Bind to MSCRAMM A Domains by Unknown Mechanisms

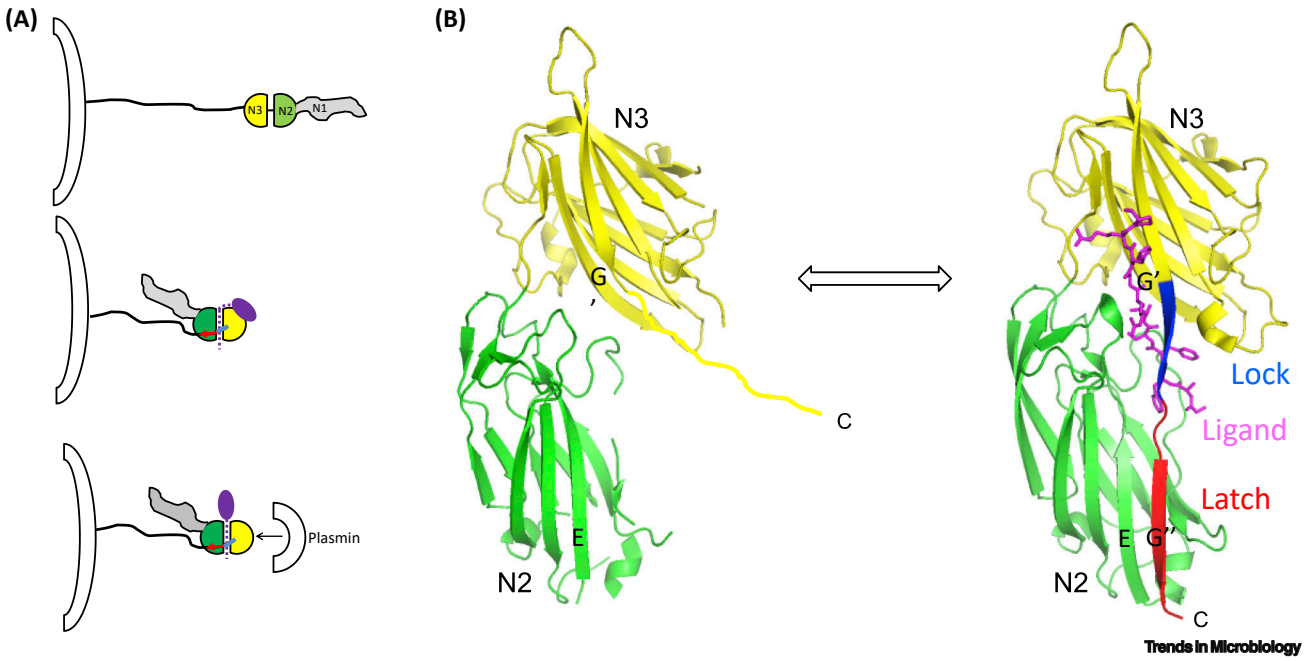

Figure 2. Ligand Binding by the Dock-Lock-Latch (DLL) Mechanism.

(A) Schematic diagrams of the interaction of ligands with the microbial surface components recognizing adhesive matrix molecules (MSCRAMMs) A domain (Clf-Sdr-FnBP family). The top diagram shows the MSCRAMM in the unbound apo form. When the peptide ligand (purple dashed line) binds, a conformational change occurs (middle diagram), resulting in the unstructured sequence immediately C terminal to N3 in the apo form capturing the ligand (the lock, blue) and undergoing β-strand complementation (red arrow) (shown in detail in B). The Fg second binding site on the N3 domain of ClfA is indicated. The lower diagram shows Fg binding by DLL to fibronectin-binding proteins (FnBPs) that promotes access of plasminogen to subdomain N3. A second binding site for Fg in FnBPs is unlikely. (B) X-ray crystal structure of the apo form of the MSCRAMM SdrG with an open trench between subdomains N2 and N3. Upon binding of the Fg β-chain peptide the disordered C terminal extension of N3, which is not part of the apo form crystal structure, locks the ligand in place (blue) and forms the latch (red). Important β-strands are indicated (G,E). Adapted from [1].

The collagen-binding protein Cna of *S. aureus* is the archetype of a family of structurally related proteins. The A domain comprises three subdomains but, in contrast to the ClfA-Sdr family, subdomains N1 and N2 bind ligands by a variant of DLL called the CH (see below) (Figure 1). Cna proteins also have B repeats but lack a C terminal unstructured region. The B repeats lack sequence similarity to the Clf-Sdr B repeats but modeling suggests that they have similar structural organization [8]. Several Gram-positive bacteria, including enterococci, streptococci, and bacilli, have structural and functional homologues of Cna [10–12].

Finally, a group of Srr proteins from streptococci contain a single IgG-like folded domain related to those that occur in MSCRAMMs. This promotes ligand binding by novel mechanisms [13].

Ligand Binding by DLL

The DLL mechanism of ligand binding by the Clf-Sdr MSCRAMMs was first elucidated for SdrG of *S. epidermidis* binding to the β-chain peptide of fibrinogen (Fg) (Figure 2) [14]. First, a short disordered segment of the Fg β-chain binds to the hydrophobic trench located between the SdrG N2 and N3 subdomains. The specificity of binding is determined by the nature of side chains of residues both in the ligand and in the binding trench. Hydrophobic residues in the ligand peptide recognize hydrophobic residues in a pocket within the trench. β-Strand complementation occurs with the G′ strand in subdomain N3 mainly through multiple backbone–backbone hydrogen bonds. This triggers a conformational change that results in the short unstructured peptide extension emanating from the C terminus of the N3 domain (the latch) forming an additional β-strand (called G″) binding to β-strand

E in one of the β-sheets in the N2 subdomain (the latching trench). The conserved TYTFTDYVD motif forms part of the latching trench. Additional contacts with the ligand peptide occur via side chains which form the lock. The β-chain peptide is oriented in a screw-like fashion with multiple backbone–backbone hydrogen bonds occurring between the peptide and residues in the MSCRAMM [15]. Separation of SdrG from its bound ligand requires these H-bonds to be broken simultaneously and involves forces equivalent to those needed to break a covalent bond, as revealed by atomic force microscopy (AFM) and simulations [15,16]. This can be likened to trying to separate Velcro by pulling laterally. Completing DLL results in the reorientation of the A domain with respect to the bacterial cell surface and projects the N3 subdomain furthest from the cell (Figure 2).

The strong forces required to separate SdrG from Fg were also seen when AFM was employed to investigate ClfA binding to Fg and ClfB binding to loricrin [17,18]. Classical assays of protein–protein interactions measure binding constants at equilibrium. AFM employs cantilever tips that have been functionalized with a single living cell or with recombinant MSCRAMM ligands being lowered onto a surface coated with the ligand or a cell and then being withdrawn. The initial binding of the MSCRAMM to the ligand involves weak bonds. The strong bonds that occur after completion of DLL are potentiated by shear stress, which implies that mechanical shearing forces induce the conformational changes as in so-called catch bonds [19]. The biological significance of this is that bacteria can be tethered to surfaces in the presence of moving fluids, for example in the blood stream.

DLL: Variations on a Theme

Several variations to the original DLL mechanism have been described. Binding to the apo form of an MSCRAMM can occur with the ligand peptide oriented in the same (parallel) direction as amino acids in subdomain N3 β-strand G′ in the ligand-binding trench (SdrG) or in the antiparallel orientation (ClfA and ClfB) resulting in the parallel or antiparallel β-strand complementation [14,20,21].

In most instances the binding residues in the peptide ligand are flanked by additional residues which results in the peptide only being able to bind to the unlocked apo form. In the case of ClfA, where the binding site is at the extreme C terminus of the γ-chain of Fg (Figure 2), the peptide can bind to both the unlocked apo form and the closed form of the MSCRAMM [21]. The Fg γ-chain peptide can penetrate the hole formed by the lock peptide covering the unoccupied ligand-binding trench.

There are two distinct binding sites for ClfA in fibrinogen. In addition to the γ-chain peptide that binds by DLL to the trench located between subdomains N2 and N3, a second binding site is located on the 'top' of subdomain N3 (Figure 2) [22]. Modeling suggests that this binds to the γ-globule of the D domain of Fg. The epitope of a monoclonal antibody (Mab) that blocks Fg binding extends across the top of N3 and covers the second Fg binding site. The Mab blocked Fg binding to recombinant ClfA *in vitro* quite weakly and did not interfere at all with binding of a truncated γ-chain peptide which could still enter the trench between N2 and N3. Furthermore, altering residues in the second binding site reduced binding to intact Fg but not the γ-chain peptide. It is possible that other MSCRAMMs that bind to the same site in Fg also use a similar cooperative two-binding-site mechanism and, indeed, other MSCRAMM–ligand interactions might also exhibit similar complexity.

In the apo form of SdrE the ligand-binding trench is 'closed' because it is occupied by an extended loop that connects β-strands A and B in subdomain N2 (loop A–B) [23]. In order for SdrE to bind the C terminal strand of complement factor H domain 20 (CD20) the SdrE loop A–B must be displaced and rotated 180°. Simultaneously, a conformational change occurs in CD20, allowing the C terminal strand to be 'clamped' and finally bound by the classic DLL mechanism. The variation of DLL is called 'closed DLL'.

The Collagen Hug

The archetype of collagen-binding protein subfamily of MSCRAMMs is Cna which binds to collagen by the CH mechanism (Figure 3) [24]. Similar to DLL, the CH involves major conformational changes to trap the collagen triple helical peptide between subdomains N1 and N2 of Cna. This is followed by a

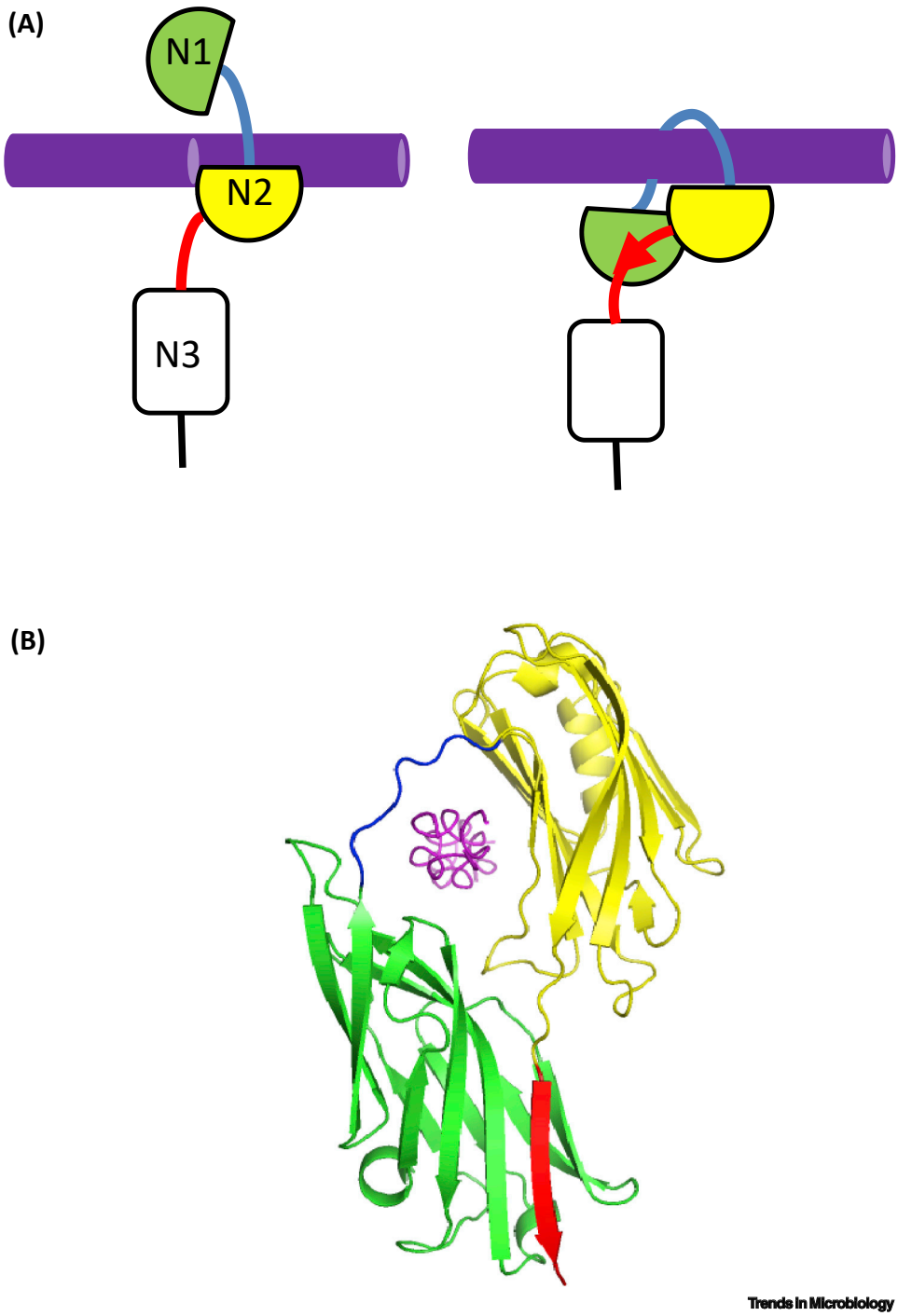

Figure 3. Cna Binds Collagen by the Collagen Hug.
(A) The N1 and N2 subdomains of Cna are separated by an extended loop (blue) that facilitates the microbial surface components recognizing adhesive matrix molecules (MSCRAMMs) binding to the triple helical collagen protein. A peptide separating N2 and N3 (red) undergoes β-strand complementation with a β-strand in subdomain N2 that locks the ligand in place. (B) The ribbon diagram of the closed locked form of Cna in complex with collagen.

locking mechanism involving β-strand complementation by a peptide extension of N2 with sequences in subdomain N1. The ability of Cna to bind the thick collagen triple peptide bundle is accommodated by the large loop separating subdomains N1 and N2. The amino acid sequence of this region is crucial for determining the affinity of the MSCRAMM for the ligand.

Like DLL, the application of AFM to study Cna–ligand interactions has revealed both weak and strong binding [25,26]. The initial interaction between Cna and its ligands involves weak forces, but once the CH is completed strong forces equivalent to those needed to break a covalent bond are needed. The interaction of Cna with laminin and complement protein C1q only involves weak forces, and the full hug does not seem to be implicated [25].

MSCRAMMs Bind a Variety of Ligands

The A domains of MSCRAMMs can bind to a diverse array of host ligands (Tables 1 and 2). Binding can be by using DLL or the CH, but in many cases the molecular basis of binding has not been determined. Important recent advances in understanding came from investigating binding of plasminogen and histones to *S. aureus* that turned out to be promoted by FnBPs.

The MSCRAMMs SdrC and the FnBPs can also engage in homophilic interactions that promote aggregation of cells and contribute to biofilm formation [27–29]. Homophilic interactions involve weak binding between individual molecules [30,31]. Multiple interactions occur between MSCRAMMs on adjacent cells that cumulatively result in strong cell–cell binding. In the case of SdrC the homophilic binding sites are two short peptides on the surface of subdomain N2 [27], but precise details require X-ray crystallographic analysis of dimers. This has been achieved for SraP, a member of the serine-rich protein family (Figure 1) where cadherin-like domains occur in the place of the MSCRAMM domains in Srr and PsrP [32].

FnBPs Binding to Plasminogen

S. aureus can capture plasminogen from serum and allow it to be converted by host or bacterial plasminogen activators to the potent serine protease plasmin. This can degrade opsonins and facilitate spreading of bacteria in infected tissue [33–35]. Several sortase-anchored CWA proteins contribute to plasminogen capture, including FnBPA and FnBPB [36]. Plg binding by these MSCRAMMs does not involve DLL. A single subdomain of the A region was sufficient to promote binding: subdomain N2 in the case of FnBPA, and subdomain N3 with FnBPB.

AFM revealed that binding of Plg to FnBPA and FnBPB involves weak bonds [37]. Remarkably, the interaction of FnBPB and Plg was strengthened considerably (tenfold) when FnBPB expressed on the bacterial cell surface was exposed to fibrinogen. It seems likely that the conformational change that occurred upon fibrinogen binding by DLL exposed or created a high-affinity Plg binding site in the FnBP and might also involve contact with the bound Fg (Figure 2).

FnBPB Binds and Protects from Histones in Neutrophil Extracellular Traps

When neutrophils are activated they release their nuclear DNA in the form of large web-like structures called neutrophil extracellular traps (NETs) [38,39]. Cytosolic and granular proteins, including neutrophil elastase, myeloperoxidase, antimicrobial peptides, and histones, are contained within the scaffold of decondensed chromatin. Histones have antimicrobial activity and can damage bacterial membranes in a similar fashion to antimicrobial peptides [40]. Wild-type *S. aureus* is resistant to histones *in vitro* and to the bactericidal activity of NETs [41]. Binding of histones occurs exclusively to FnBPB and most likely occurs by DLL. The affinity of FnBPB for histone H3 is 20-fold higher than for fibrinogen, which indicates that FnBPB will bind histones preferentially when both proteins are present. Furthermore, FnBPB could bind both H3 and plasminogen. Activation of bound plasminogen resulted in cleavage of H3. Thus, FnBPB is the major CWA protein promoting resistance to histones, and it does so by a dual mechanism involving capturing histones and preventing access to the cell surface and simultaneously binding plasminogen which, when activated to plasmin, can destroy the sequestered inhibitor.

The Role of MSCRAMMs in Staphylococcal Infection and Host Colonization

MSCRAMMs have a variety of roles in infection and host colonization (Table 3). Recent advances are discussed below. They promote bacterial adhesion to host tissue and cells, survival in the blood stream during the bacteremic phase of invasive infection, and the formation of abscesses in the skin and in internal organs.

Infection or colonization model	MSCRAMM[a]	Role in pathogenesis	Refs
Colonization	ClfB	Adhesion to nasal squames via loricrin and colonization of mouse nares	[53]
		Colonization of human nares	[50]
		Adhesion to squames from eczema patients' skin	[55,57]
	SdrC SdrD	Adhesion to nasal squames, ligand unknown	[88]
Subcutaneous abscess	ClfA FnBPs	Abscess development and bacterial burden	[89]
Dermonecrosis	ClfB	Abscess development and pathology. Binding to loricrin in developing abscess wall	[59]
Septic death	ClfA	Enhanced mortality following iv injection	[90–92]
Bacteremia and kidney abscess	ClfA ClfB SdrD SdrE	Enhanced survival from neutrophils in blood stream following iv inoculation and/or kidney abscess formation	[90]
Bacteremia and joint infection. Septic arthritis	ClfA Cna	Enhanced survival from neutrophils in bloodstream following iv inoculation and/or invasion of joints	[91,93]
Endocarditis	ClfA, ClfB	Adhesion to catheter-induced thrombus	[43,45]
	FnBPA	Adhesion to catheter-induced thrombus, invasion of endothelium adjacent to infected thrombus	[44]
Endovascular infection	ClfA	Adhesion to mouse mesenteric vein endothelium via integrin $\alpha_v\beta_3$ and von Willebrand factor	[47,48]
Foreign body infection	FnBP	MRSA biofilm-associated infection	[94]
	Staphylococcus epidermidis SdrF	Adhesion to explanted ventricular assist device membrane/driveline	[95]
	Staphylococcus aureus ClfA FnBPs		[96]
	FnBPs ClfA	Mouse aortic patch colonization	[97]
	ClfB	Catheter-associated urinary tract infection	[58]
Meningitis	*Streptococcus agalactiae* Srr1/Srr2	Survival in mouse blood and infection of brain	[6]
Ocular keratitis	Cna	Enhanced colonization and infection in rabbits	[98]
Joint infection	Fibrinogen-binding MSCRAMMs	Biofilm formation in synovial fluid	[99]
Mastitis	FnBPs	Invasion of epithelial cells in mammary gland	[100]
Urinary tract infection	*Staphylococcus saprophyticus* SdrI	Persistence in mouse urinary tract	[101]

Table 3. MSCRAMMs Involved in Host Colonization and Pathogenesis

[a] *Staphylococcus aureus* unless otherwise stated.

ClfA Plays a Central Role in *S. aureus* Endovascular Infections

Infective endocarditis (IE) is a serious complication of *S. aureus* bacteremia [9]. IE is difficult to treat and results in high mortality. Indeed, the incidence of *S. aureus* IE and mortality from such infections have been increasing [42].

Heart-valve endothelium that has been damaged by trauma or inflammation is prone to infection. Until recently it was assumed that bacteria could rarely colonize previously undamaged endothelial surfaces, but their ability to do so was difficult to demonstrate experimentally. Endocarditis infection models in rabbits and rodents involve inserting a catheter into the carotid artery to stimulate damage to the aortic valve causing a small sterile thrombus to which bacteria could adhere [43,44]. Most models involve leaving the catheter in place during infection, which means that, in part, they involve a foreign body infection. Fibrinogen-binding MSCRAMMs ClfA, ClfB, and FnBPs contribute to attachment to the thrombus [43–45], while subsequent tissue infection requires bacteria to be able to invade endothelial cells via FnBPs forming a fibronectin bridge to a fibronectin binding $\alpha5\beta1$ integrin which stimulates uptake [44,46] in a manner that is promoted by mechanical shear forces [46].

S. aureus can interact directly with cultured endothelial cells in a flow chamber and to the surface of endothelial cells of mouse mesenteric veins in an *in vivo* colonization model. *S. aureus* can adhere to endothelial cells via a fibrinogen bridge formed between ClfA on the bacterial cell surface and the $\alpha_V\beta_3$ integrin on the endothelial cell [47] (Figure 4). This occurred under shear stress typical of flowing blood, recalling that the DLL mechanism of ClfA binding to Fg is enhanced under these circumstances. It seems likely that that interaction of Fg with the $\alpha_V\beta_3$ integrin is strengthened by shear-forces as occurs with FnBP-Fn binding to the $\alpha_5\beta_1$ integrin [46]. This triggers release of von Willebrand factor (vWBF) which provides further support for bacterial attachment. A complex two-factor bridge forms between ClfA and the $\alpha_V\beta_3$ integrin that involves bacterial vWBF binding protein (vWBFBP) and vWBF [48] (Figure 4). vWBFBP binds ClfA with high affinity, but whether this involves DLL is not known. Circulating vWBF binds to damaged endothelial surfaces where the underlying extracellular matrix (ECM) containing collagen is exposed. Thus, *S. aureus* adheres to previously undamaged endothelium, and exposed ECM by the same mechanism.

Recently, a novel murine model of endocarditis was reported which involves short-term catheterization to trigger damage, withdrawal of the catheter, and subsequent infection [49]. It was possible to trigger inflammation by introducing histamine through the catheter directly onto the heart endothelium prior to its withdrawal. Damage without inflammation allowed *S. aureus* to adhere in a ClfA- and vWBFBP-dependent manner seen in the endothelial cell and mesenteric vein experiments. However, inflammation promoted platelet deposition. Bacteria bound the platelet-rich thrombus independently of sortase-anchored wall-associated proteins.

It can be concluded that several different mechanisms, that are not mutually exclusive, contribute to the initiation and development of IE, and that MSCRAMMs, particularly ClfA, are crucially important.

New Insights into the Functions of ClfB

Clumping factor B ClfB binds to Fg, cytokeratin 10, and loricrin [20]. The last two proteins occur abundantly in squamous epithelial cells (corneocytes) in the outer layer of skin. A major function of ClfB appears to be in nasal colonization by promoting adhesion to corneocytes from the moist squamous epithelium of the nose [50–52]. Nasal colonization in human volunteers and in a mouse model was shown to be dependent on expression of ClfB by *S. aureus*, and in the case of the latter by the presence of loricrin in the nasal tissue of the host [50,51,53]. Recently there have been several important advances in understanding ClfB's roles in the interactions of *S. aureus* with the host.

Colonization of Skin of Atopic Dermatitis Patients

Atopic dermatitis (AD) or eczema is a common chronic inflammatory skin disorder. *S. aureus* is regarded as a transient resident of healthy skin but is able to proliferate on AD skin [54]. The presence of *S. aureus* exacerbates inflammation. *S. aureus* strains isolated from AD skin adhere more strongly

to the ClfB ligand loricrin than do isolates from healthy nasal carriers [55]. Strong adhesion to loricrin by a strain from the commonest clonal complex associated with AD is dependent on ClfB.

The most severe forms of AD occur in patients with low levels of natural moisturizing factors (NMFs) that are breakdown products of the corneocyte protein filaggrin. Loss-of-function mutations affect filaggrin structure [54]. Also, filaggrin expression is reduced by Th2 inflammation that occurs in AD. NMF corneocytes have an abnormal morphology, with villous-like projections occurring across the normally flat surface [56,57].

Adhesion of *S. aureus* to corneocytes with low levels of NMFs is much stronger than to those with high NMFs [57]. AFM demonstrated that adhesion occurs across the entire surface of the corneocyte and appears to associate with the tips of the villous-like projections. This involves strong forces that were also observed when ClfB bound loricrin *in vitro* by DLL. Thus, ClfB is a crucially important adhesin for the deformed corneocytes in the skin of AD patients, and binding by ClfB to its corneocyte ligand(s) likely occurs by DLL.

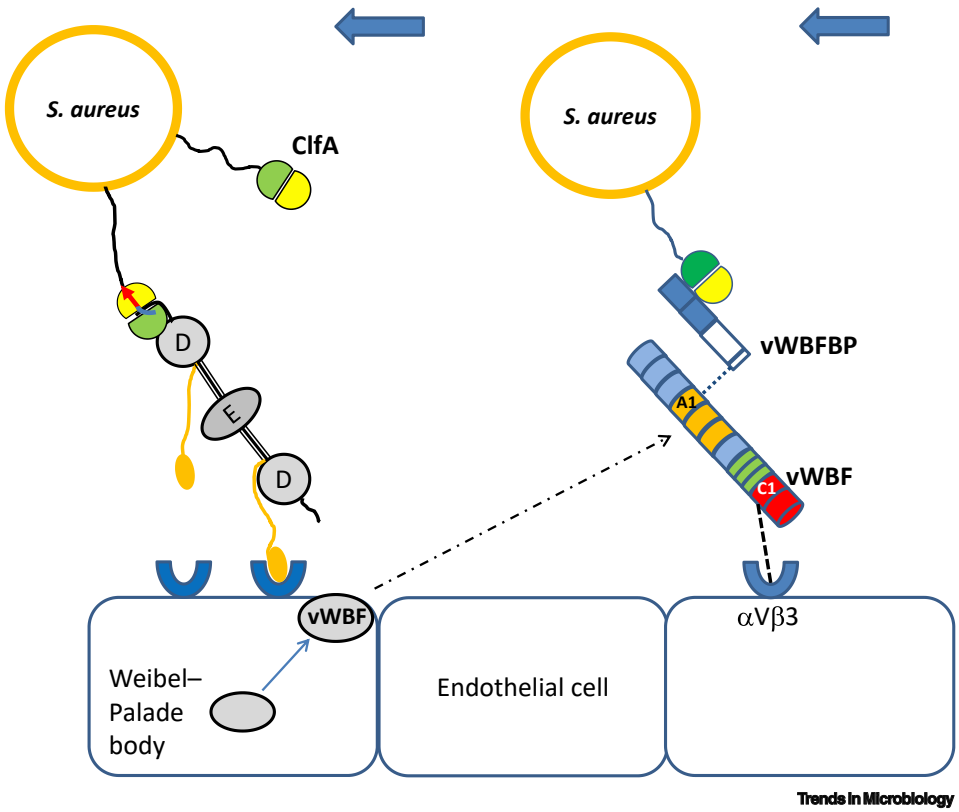

Figure 4. Clumping Factor A Promotes Interactions with the Endothelium.
Clumping factor A can initiate *Staphylococcus aureus* adherence to undamaged endothelial surfaces via a fibrinogen bridge between the bacterial cell and the $\alpha_V\beta_3$ integrin on the endothelial cell surface. It is likely that this interaction is potentiated by shear forces (blue arrow). The figure on the left shows ClfA engaging with the Fg D domain via dock-lock-latch (DLL) while the Aα chain of Fg binds to the integrin. *S. aureus* can also bind to the endothelium (or exposed extracellular matrix in damaged endothelium) via a bridge formed between ClfA and von Willebrand factor-binding protein (vWBFBP), von Willebrand factor, and the $\alpha_V\beta_3$ integrin on intact endothelium or exposed collagen on damaged endothelium.

Catheter-Associated Urinary Tract Infection

Catheter-associated urinary tract infection (CAUTI) caused by *S. aureus* is an emerging disease that can lead to bacteremia and sepsis. Catheterization through the urethra causes inflammation and leads to fibrinogen deposition on the implant and the bladder surface [58]. This is associated with an increased risk of bacterial infection, including by *S. aureus*. Infecting bacteria were observed in close association with fibrinogen deposits, implying that the ability to attach to deposited fibrinogen is important in initiating infection. In a mouse model of CAUTI, ClfB-deficient bacteria colonized catheter surfaces less well than did the wild-type, and a small but significantly lower number of bacteria occurred in the bladder. No difference was seen with a ClfA mutant. Why the major Fg binding MSCRAMM ClfA did not feature as a virulence factor in the CAUTI model is unclear. It was suggested that growth of *S. aureus* in urine might lead to differential expression of MSCRAMMs, or the presence of substances in urine might affect MSCRAMM function.

Skin Abscess Formation

S. aureus is a frequent cause of skin abscesses. Community-associated methicillin-resistant *S. aureus* (CA-MRSA) strains cause particularly severe skin lesions referred to as severe skin and soft-tissue infections (SSSTIs). In a mouse model, ClfB was found to be an important factor in the early stages of abscess development by the CA-MRSA strain LAC where a ClfB-deficient mutant had altered abscess structure and a reduced bacterial burden was evident [59]. Immunohistochemical analysis revealed that loricrin, which is normally only expressed in skin corneocytes, was present in the abscess wall. Infection of loricrin knockout mice resulted in smaller abscesses with reduced pathology and a lower number of infecting bacteria, implying that the ClfB–loricrin interaction is important in abscess development.

Concluding Remarks

Molecular and structural biology, together with AFM, have provided important advances in understanding MSCRAMM–ligand interactions. The ability to study the binding of a single bacterial cell to immobilized ligands, or to probe MSCRAMM–ligand interactions with purified proteins, has revealed that both weak and strong interactions occur in the canonical DLL and CH mechanisms. The initial binding is quite weak, but once the DLL or CH conformational change has taken place under mechanical stress the molecules can only be separated by applying forces equivalent to those needed to break a covalent bond. This is reminiscent of catch bonds involved in pilus–ligand interactions [19]. Furthermore, shear stress stimulates the conformational changes, revealing that bacteria can attach firmly to the matrix when fluids are flowing rapidly, such as in the blood stream or in nasal mucous. Many backbone–backbone H-bonds must be broken simultaneously for separation to occur.

Recent studies have revealed that ClfB is an important virulence factor in the pathogenesis of skin abscesses. The role of ClfB occurs in early abscess development and is due to its ability to bind to the corneocyte protein loricrin, the expression of which is dysregulated in damaged skin so that this occurs in the early abscess wall. This makes ClfB an attractive target as a vaccine candidate to prevent SSSTIs.

ClfB is important in colonization of the moist squamous epithelium of the anterior nares where loricrin is also the important ligand. ClfB also promotes adhesion to, and proliferation of, *S. aureus* on the skin of eczema patients. Deformed corneocytes from severe cases of eczema with low levels of natural moisturizing factors strongly bind bacteria in a ClfB-dependent fashion. It appears that bacteria adhere to tips of villous-like projections on low-NMF corneocytes. This implies the presence of loricrin in the projections or that bacteria can bind to a component of corneodesmosomes which are abnormally present in the projections. This makes ClfB an attractive target for blocking *S. aureus* skin colonization to prevent or treat AD.

The number of ligands recognized by MSCRAMMs has expanded substantially. Some involve DLL but others do not. FnBPs bind host plasminogen, but one or more other sortase-anchored protein(s) also bind this host ligand as well as moonlighting cytoplasmic proteins. In contrast, FnBPB is the only CWA

Outstanding Questions

Are ligands other than loricrin involved in adherence of *S. aureus* to corneocytes in AD patients?

Can antiadhesion approaches be employed to prevent *S. aureus* colonization of the nares or skin of AD patients?

What are the mechanisms underlying shear-stress-dependent binding of MSCRAMMs to their ligands?

Does vWBF-binding protein bind ClfA by DLL?

protein that binds histones where it reduces access of the antimicrobial proteins to the bacterial membrane and facilitates plasminogen capture to facilitate their destruction.

In conclusion, MSCRAMMs perform many functions that are essential for colonization of, and survival within, the host. Recent structural and functional analysis has defined the mechanistic basis of these interactions and provides a framework for future studies (see Outstanding Questions).

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