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Neutrophil extracellular traps in bacterial infections and evasion strategies

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Neutrophils are innate immune cells that have a vital role in host defense systems. Neutrophil extracellular traps (NETs) are one of neutrophils' defense mechanisms against pathogens. NETs comprise an ejected lattice of chromatin associated with histones, granular proteins, and cytosolic proteins. They are thought to be an efficient strategy to capture and/or kill bacteria and received intensive research interest in the recent years. However, soon after NETs were identified, it was observed that certain bacteria were able to evade NET entrapment through many different mechanisms. Here, we outline the recent progress of NETs in bacterial infections and the strategies employed by bacteria to evade or withstand NETs. Identifying the molecules and mechanisms that modulate NET release will improve our understanding of the functions of NETs in infections and provide new avenues for the prevention and treatment of bacterial diseases.

KEYWORDS

neutrophil, neutrophil extracellular traps, bacterial infection, mycoplasma, NETs evasion, DNase

1 Introduction

Neutrophils are the most prevalent type of leukocytes circulating in the blood and are crucial for maintaining health. They differentiate from hematopoietic stem cells and are discharged from the bone marrow when terminally mature. They are the first cells to leave circulation and migrate to the infection site during an immunological challenge. There, they eliminate bacteria, communicate damage status to other immune cells, and are involved in the healing process (1). Much is known about the antimicrobial response of neutrophils. They are highly skilled in phagocytosis, which is their first vital mechanism for the eradication of disease-causing pathogens and elimination of dead cells and tissue debris

(2, 3). The second mechanism for eliminating pathogens is degranulation, which involves regulation of the immune system response via the release of various granules (4–6).

Approximately 20 years ago, a new mechanism by which neutrophils fight infections was termed neutrophil extracellular traps (NETs) (7). This involves the loosening of chromatin in the neutrophil nucleus and forming complexes with granular and cytoplasmic proteins, which are then released into the extracellular environment. There, NETs encapsulate and kill microorganisms, and block their dissemination (7, 8).

2 NETs

NETs are a special form of programmed cell death, which is distinct from other cell death forms (apoptosis, necroptosis, and pyroptosis). In general, the complex process of NET formation begins with the recognition of microorganism, triggering the activation of the NETs pathway. This, in turn, leads to the breakdown of the nuclear membrane and the release of decondensed nuclear DNA into the cytoplasm. As this DNA mingles with cellular components including the histones, granules and cytoplasmic proteins, the process culminates in the rupture of the plasma membrane and the ultimate release of the NET structure into the extracellular space. Simultaneously, these traps are capable of degrading virulent bacterial factors (9–11).

2.1 NETs stimulation and signaling receptors

NET release is triggered by various stimuli. A range of bacterial species induce NET release. For Gram-positive bacteria, such as *Staphylococcus aureus* (7, 12, 13), *Streptococcus pyogenes* (14, 15), *Streptococcus pneumoniae* (16), *Streptococcus agalactiae* (17), *Streptococcus sanguinis* (18), *Streptococcus suis* (19). For Gram-negative bacteria, such as *Escherichia coli* (20–22), *Salmonella typhimurium* (7), *Shigella flexneri* (7), *Haemophilus influenzae* (23), *Pseudomonas aeruginosa* (24, 25), *Yersinia pseudotuberculosis* (26), *Photobacterium luminescens* (27). In addition, other bacterial species, including *Mycobacterium tuberculosis* (28, 29), *Mycobacterium canettii* (28), *Mycobacterium avium* (30), and *Mycoplasma bovis* (31). Furthermore, bacterial components like lipopolysaccharide (LPS) (7), flagella (25), bacterial toxin nigericin (17), and calcium ionophore A2318 (17) are also involved in NETs stimulation. Additionally, diverse inflammatory mediators including interferon (IFN)- α (32), IFN- γ (32), interleukin (IL)-8 (7), IL-1 β (33, 34), IL-2 (35), IL-6 (36), IL-10 (36), tumor necrosis factor (TNF)- α (33, 37), granulocyte-macrophage colony-stimulating factor (GM-CSF) (38), transforming growth factor (TGF)- β (34), and complement factor 5a (C5a) (32, 38) have been shown to stimulate NET release.

Moreover, Neutrophil receptors play a crucial role in activation of neutrophil and formation of NETs. The specific engagement of cell receptors by extracellular signaling molecules activates diverse intracellular signaling cascades and regulate NETs functions. In response to different bacterial triggers, NETs can release by the

activation of different receptors including toll-like receptors (TLRs) (39–44), nucleotide-binding oligomerization domain-like receptors (NLRs) (45), C-type lectin receptors (CLRs) (46), complement receptors (CRs) (47), Fc receptors (47–50) and other neutrophil receptors like protease activated receptor-2 (PAR-2) (51).

2.2 NET components

The composition of NETs varies depending on the stimuli, and is primarily made up of DNA and histone proteins (H1, H2A, H2B, H3, and H4), which are originated from the nucleus followed by granular proteins that are normally stored in distinctive neutrophil granules in the cytoplasm of neutrophil such as neutrophil elastase (NE), myeloperoxidase (MPO), defensins, and cathepsin G from primary granules, lactoferrin, cathelicidins, and lysozyme C from secondary granules, and gelatinase from tertiary granules, as well as other proteins such as calprotectin and proteinase 3 are located in the cytoplasm of neutrophils (7, 52–54) (Supplementary Table S1).

2.3 Mechanisms of NETs formation

NETs were first reported in 2004 and were primarily described as a cell death process in activated neutrophil (7). When DNA leaks extracellularly, not all NET developments result in cell death, and not every neutrophil death necessarily results in NET formation. “NETosis” is often employed throughout research for referring to NET formation, which can be categorized to as “lytic” and “non-lytic” forms.

2.3.1 Lytic mechanism

The “lytic” mechanism of NET formation is the interaction between stimuli and cell receptors, which triggers Raf-MEK-ERK signaling and activates the NADPH oxidase complex (55). This complex produces peroxide ions in neutrophils, increasing levels of cytosolic reactive oxygen species (ROS). MPO detects this rise and is often paired with other proteases to form the azurosome. MPO trigger the activation and translocation of NE from azurophilic granules to the nucleus, where elastase proteolytically processes histones to disrupt chromatin packaging (56, 57). MPO then binds to chromatin and synergizes with NE to decondense chromatin independently of its enzymatic activity (57). The nucleus expands along with its chromatin, and cell lysis occurs because of gasdermin D, which can be activated by serine proteases in neutrophil inducing pore formation in the cell membrane (58). NETs are extruded into the extracellular space after membrane rupture and cell death within 3–8 h of neutrophil activation (9, 59).

2.3.2 Non-lytic mechanism

The “non-lytic” or vital mechanism, involves increasing the concentration of cytosolic calcium through calcium ionophores, which activate the protein arginine deiminase 4 (PAD4) that leads to citrullates arginine histone residues, and reduces their positive charge. Histones then begin to lose their electrostatic attraction to DNA, and the chromatin expands along with the nucleus (37, 60). This oxidase-

independent mechanism occurs within minutes of gram-positive skin infections; the cells release NETs during crawling without lysis, which prevents systemic bacterial dissemination (13, 61). However, vital NET formation might be more closely associated with infection than previously thought because soon after releasing NETs, neutrophils are still viable and can carry out additional host response processes, such as phagocytosis, chemotaxis, and microbial killing (62). In addition to non-lytic NETs with nuclear DNA release, NETs composed of mitochondrial DNA, NE, and are first described in GM-CSF-primed neutrophils stimulated *in vitro* with LPS or C5a (38, 63) since this process would not require neutrophil lysis, which would enable phagocytosis to continue (10).

2.3.3 Other forms of NETs

However, divergent views have persisted in this field. NETs can form in the absence of PAD4 and citrullinated histone 3 (64, 65). It can also occur during leukotoxic hypercitrullination (LTH), defective mitophagy, and organ injury (66). Other types of NETs have also been described, including cloudy NETs, spiky NETs, aggregated NETs, and bicarbonate-induced aggregated NETs (67). Therefore, we cautiously take opinions about these studies into consideration

3 Effects of NETs in bacterial infections

3.1 Morphological effects

NETs have various effects on the morphology of bacteria, including physically trapping and immobilizing them, leading to changes in their morphology as they become entangled in the web-like structure of the NETs (7). Additionally, they can release DNA, enzymes, and antimicrobial proteins that can damage the cell walls of bacteria and/or membranes, leading to changes in their morphology as they become structurally compromised (68–70). Furthermore, NETs are involved in the disruption of bacterial biofilms, which can also lead to changes in the morphology of the bacteria (71).

3.2 Functional effects

Along with the impact of NETs on the shape of bacteria, they can kill and limit the growth of bacteria and prevent their spread in the environment. They possess antimicrobial properties with components such as DNA, histones, granules, and cytoplasmic proteins that have bactericidal effects (7, 68, 72–75). Interestingly, NETs play an important role in the defense against bacteria, even in the absence of microbicidal activity. These infections are ensnared but not eliminated by NETs (28, 76–79), indicating that NET-mediated microbial trapping alone plays a substantial role in immune defense.

As mentioned above, the formation of NETs and their effect on bacterial infection are mostly reported *in vitro* conditions. However, there is limited research describing the stimulation of NETs in response to bacterial infection *in vivo*. It is difficult to verify NETs *in vivo* because it calls for specialized technical knowledge. Besides, it

is hard to assess the kind of stimulus, its dosage, and its exposure duration *in vivo*. Researchers may use genetically modified animal models to study the role of specific proteins or signaling pathways in the regulation of NET formation during bacterial infection (80).

Furthermore, the composition of NETs determines their efficiency. Mice exposed to low concentrations of cathepsin G are more susceptible to infection with the Gram-positive bacterium *S. aureus* (81), whereas those exposed to low concentrations of NE are more susceptible to Gram-negative bacteria such as *E. coli*, *K. pneumoniae*, and other *Enterobacteriaceae* (70, 81). Additionally, the antimicrobial response of NETs is influenced by the environment in which they are developed; NETs under static conditions show limited bacterial killing, whereas those under dynamic conditions show enhanced bacterial trapping and reduced killing (78).

Although NETs protect the host against microbes, there are diseases and conditions that can interfere with the release of NETs. Some examples of diseases that can affect NET release or neutrophil function are autoimmune diseases, chronic inflammatory conditions and sepsis, which can alter the function of neutrophils and their ability to release NETs. In these conditions, the dysregulation of neutrophil function and NET release can contribute to the pathology of the disease and affect the body's ability to fight infections and maintain immune homeostasis (82, 83).

4 Modulation of NET release in bacteria

As mentioned before, the release of NETs is essential for defense against pathogens; the evasion of NETs appears to be a widespread strategy to allow pathogen proliferation and dissemination and is currently a topic of intense research interest. Here, we review the current knowledge of evasion strategies used by bacteria to dysregulate NET formation and functions.

4.1 NET formation inhibition

Specific molecules and pathways that inhibit NET release. Thus, NET inhibition mechanisms in bacterial infections are summarized in this section of the review (Table 1).

4.1.1 Downregulation of NET-stimulating phenotypes

Suppression of phenotypes that trigger NET release is a way to prevent their formation. Flagellum is the main bacterial component required to trigger maximal NET release, and flagellum-deficient bacteria remain seriously impaired in triggering NET formation (25). In addition, LasR-deficient *P. aeruginosa* strains harbor a limited capability to trigger neutrophil DNA release due to reduce the expression of elastase LasB and proteases LasA. The neutrophil NADPH oxidase pathway is required to decrease NET release caused by LasR-deficient strains, but it is not dependent on downstream quorum sensing pathways, LPS synthesis, or bacterial motility (84).

4.1.2 Inhibition of NET-triggered molecules

IL-8 is a prominent neutrophil chemoattractant and activator that induce NET formation (7). However, group A *Streptococcus* (GAS) protease SpyCEP (also called ScpC) cleaves IL-8 and reduces neutrophil production of extracellular traps (86). In addition, streptolysin O toxin (SLO) prevents the release of IL-8 and elastase from neutrophils, blocks NET formation, and inhibits NETs by dissolving cell membranes and fibrous extracellular DNA strands (87).

4.1.3 Suppression of NET-mediated receptors on neutrophil

Neutrophil surface receptors have been linked to suppression of NET formation. GAS expresses a high-molecular-weight hyaluronic acid capsule (HMW-HA). hSiglec-9 specifically binds to HMW-HA through a region of its terminal Ig-like V-set domain distinct from the Sia-binding site. HMW-HA recognition by hSiglec-9 blocks the oxidative burst and limits NET formation, thereby promoting bacterial survival (88). Moreover, the sialylated capsular polysaccharide of Group B *Streptococcus* (GBS) interacts with

neutrophil Siglec-9, dampening neutrophil responses in a Sia- and Siglec-9-dependent manner, causing a reduction in the neutrophil oxidative burst, diminished formation of NETs, and increased bacterial survival (91). In addition, β protein from GBS inhibits human leukocyte phagocytosis, oxidative burst, and extracellular trap formation by binding to hSiglec-5 in a Sia-independent manner (92). However, engagement of Siglec-14 by β -protein antagonizes the repressive effects of Siglec-5 by activating mitogen-activated protein kinase (MAPK) signaling (99). *Moraxella catarrhalis* limits ROS production by possibly binding to immunosuppressive Siglecs receptors (Siglec-5 and Siglec-9) and consequently suppressing NET generation (89). Furthermore, soluble Siglec-9 exhibited strong binding with α 2-3-linked sialoglycoproteins adsorbed by *P. aeruginosa*. The interaction between *P. aeruginosa* (+Sias) and siglec-9 on neutrophils decreases the amount of ROS and the release of elastase, which in turn decreases the formation of NETs (85). Moreover, *Acinetobacter baumannii* inhibits the formation of NETs by suppressing the surface expression of CD11a in neutrophils, thereby escaping host immune responses and contributing to the development of *A. baumannii* infections (97).

TABLE 1 Factors associated with the inhibition of NET release in bacterial infections.

Evasion strategy	Molecule (s)	Microorganism	Modulatory effect on NETs formation	References
Inhibition	Flagella	<i>P. aeruginosa</i>	Flagellum-deficient bacteria are severely impaired in triggering NET formation	(25)
	LasR		<i>P. aeruginosa</i> lacking LasR have a restricted ability to cause the release of neutrophil DNA.	(84)
	Sialoglycoproteins		Display binding to Siglec-9, reduce ROS level and elastase release, and lower the development of NETs	(85)
	SpyCEP	GAS	Cleaves IL-8, and reduces neutrophil production of extracellular traps	(86)
	SLO		Blocking IL-8 secretion and responsiveness & Dissolve cell membranes and fibrous extracellular DNA strands	(87)
	HMW-HA		Engage hSiglec-9, block oxidative burst and NET formation	(88)
	?	<i>M. catarrhalis</i>	Suppresses the ROS production, and thus inhibiting the production of NETs	(89)
	TcpC	<i>E. coli</i>	Promoting the degradation of PAD4, and reduce NET formation	(90)
	Sialylated polysaccharide	GBS	Binding to Siglec-9, suppressing ROS and reduce formation of NETs	(91)
	CPS		Binding to Siglec-5, inhibits oxidative burst, and impair NETs formation	(92)
	ACT	<i>B. pertussis</i>	Inhibit the oxidative burst by generating cAMP and consequently inhibit formation of NETs	(93)
	CyaA	<i>B. paraptussis</i>	Mediated inhibition of ROS and reduces NET activation	(94)
	LPS	<i>K. pneumoniae</i>	Involve in ROS inhibition and diminish the formation of NETs	(95)
	T3SS and CPS-I	<i>B. pseudomallei</i>	Inhibition of NADPH oxidase pathway and reduce NET release	(96)
	?	<i>A. baumannii</i>	Suppression of the surface expression of CD11a in neutrophils	(97)
WiP1	<i>S. aureus</i>	Display suppression of NET release	(98)	

P. aeruginosa, *Pseudomonas aeruginosa*; *M. catarrhalis*, *Moraxella catarrhalis*; *E. coli*, *Escherichia coli*; *B. pertussis*, *Bordetella pertussis*; *B. paraptussis*, *Bordetella paraptussis*; *K. pneumoniae*, *Klebsiella pneumoniae*; *B. pseudomallei*, *Burkholderia pseudomallei*; *A. baumannii*, *Acinetobacter baumannii*; *S. aureus*, *Staphylococcus aureus*; ROS, reactive oxygen species; IL-8, interleukin-8; SLO, streptolysin O; GAS, group A *Streptococcus*; HMW-HA, high molecular weight-hyaluronic acid; PAD4, protein arginine deiminase 4; GBS, group B *Streptococcus*; HMW-HA, high molecular weight-hyaluronic acid; PAD4, protein arginine deiminase 4; GBS, group B *Streptococcus*; Siglec-9, Sialic acid-binding Ig-like lectin-9; Siglec-5, Sialic acid-binding Ig-like lectin-5; CPS, capsular polysaccharide; ACT, adenylate cyclase toxin; cAMP, cyclic adenosine monophosphate; CyaA, adenylate cyclase; LPS, lipopolysaccharide; T3SS, type 3 secretion system; CPS-I, capsular polysaccharide-I; NADPH, nicotinamide adenine dinucleotide phosphate; WiP1, wild-type p53-induced phosphatase 1; ?, unknown.

4.1.4 Interfering of NADPH signaling and ROS formation

NET formation is related to the production of ROS, both cytosolic and mitochondrial (55, 100). The adenylate cyclase toxin (ACT) of *Bordetella pertussis* inhibits formation of NETs by generating cyclic adenosine monophosphate (cAMP), consequently inhibiting oxidative burst (93). *Bordetella parapertussis* also expresses CyaA in a Bvg-regulated manner. This toxin is released into the extracellular space, which mediates the inhibition of ROS and reduces NET activation in human-derived neutrophils (94).

K. pneumoniae ST258 is a poor inducer of ROS generation, and consequently inhibits NET formation, suggesting that the polysaccharide part of LPS is responsible for this inhibition and results in increased bacterial survival (95). *Burkholderia pseudomallei* modifies the magnitude of NET formation via the action of its type 3 protein secretion system (T3SS), encoded by the *bsa* locus, and capsular polysaccharide I (CPS-I) encoded by the *wcb* operon, which attenuates NET release by inhibiting the NADPH oxidase pathway. *B. pseudomallei* mutants defective in the virulence-associated T3SS or CPS-I induced elevated levels of NETs. NET induction by these mutants is associated with increased bacterial killing (96).

4.1.5 Others

Wild-type p53-induced phosphatase 1 (Wip1) suppresses NET release in *S. aureus* in mice model. Inhibition of Wip1 significantly suppresses the activity of *S. aureus* and accelerates abscess healing in *S. aureus*-induced abscess model mice by enhancing NET formation (98). Moreover, uropathogenic *E. coli* secretes a multifunctional virulence factor called TcpC, which primarily inhibits NETs by serving as an E3 ligase, promoting the degradation of PAD4. TcpC not only inhibits the citrullination of chromatin histones, but also affects the transcription of related genes in the nucleus and represents an additional NET evasion function of this bacterial derived virulence factor (90).

4.2 Degradation of NET components

Studies investigating the production of NET-degrading molecules by bacteria have focused largely but not exclusively on the nucleases (Table 2; Figure 1).

4.2.1 Nuclease expression

DNA forms a NET framework that holds multiple enzymes in close proximity, sometimes allowing for synergistic interactions among them (68). DNA is hydrolyzed by nucleases that belong to a group of hydrolases, which are further classified as endonucleases and exonucleases. These enzymes are involved in replication or repair of genetic material to maintain chromosome (136). However, extracellular nucleases have been reported in some bacterial species for the degradation of NET scaffold DNA, enabling bacteria to evade the NET antimicrobial mechanism, promoting pathogenicity, and dissemination to other sites in the host. For example, nuclease (Nuc) (101, 102) and extracellular adherence protein (Eap) (103, 104) are produced by *S. aureus* and interfere

with the antimicrobial activity of NETs. These proteins help *S. aureus* to escape from NET-mediated killing, impede its removal, and increase infection-related mortality. Moreover, *S. aureus* escapes this defense by converting NETs to deoxyadenosine (dAdo) via the action of Nuc and adenosine synthase A (AdsA), which triggers caspase-3-mediated death of macrophages (105, 106). Moreover, *S. aureus* synchronizes gene expression during skin infection through the ArlRS-MgrA regulatory system, which regulates nuclease expression. This cascade is required for both the appropriate structuring of the abscess and evasion of the host innate immune system, both of which are necessary for *S. aureus* virulence. In contrast, mutants lacking MgrA and ArlRS have reduced capacity to avoid NET function (107). In addition, *S. aureus* expresses the competence regulator (ComK) when exposed to ROS. ComK upregulates the expression of genes encoding the transport machinery for glucose and DNA uptake, providing extra nutrients to increase the fermentation possibility of bacteria that are unable to respire and a source of nucleotides to repair DNA damage from ROS. Bacteria may use competence-related genes to better withstand NETs, because NETs are a source of both nucleotides and ROS (108).

P. aeruginosa encodes an operon of two secreted enzymes, a DNase and a predicted alkaline phosphatase. DNase (*eddB*) contributes to the degradation of NET to defend *P. aeruginosa* against NET-mediated killing, whereas *edda* has both alkaline phosphatase and phosphodiesterase (PDase) activities that do not cause DNA degradation similar to that of DNase, but its protective function is likely a result of removing cation-chelating phosphates from the extracellular DNA phosphodiester backbone (110).

GAS is a leading cause of severe invasive disease in humans, and has evolved numerous virulence factors that aid in blocking NET function through the expression and secretion of the extracellular nuclease Sda1, which is advantageous for promoting bacterial dissemination throughout the host organism and evasion of the host innate immune response (77, 112). Similarly, *S. pyogenes* nuclease A (SpnA), a cell wall-anchored DNase, shows a unique protein architecture and promotes survival in human blood and in neutrophil killing assays, enable for the destruction of NETs and is believed to be an important immune evasion mechanism (113). A pneumococcal nuclease (EndA) acts as a virulence determinant, counteracting host-mediated trapping by NETs, thereby promoting bacterial spread from local sites to the lungs and then to the blood stream (76). Furthermore, the competence-independent activity of EndA is important for the virulence of *Streptococcus pneumoniae*, which mediates the rapid degradation of extracellular DNA and NETs (114). In addition, the secretion of nucleotide sequence-independent endodeoxyribonuclease TatD from *S. pneumoniae* is a novel potential extracellular DNase that plays a key role in evading NET-mediated bactericidal activity (115).

Streptococcus suis induces NET formation in porcine neutrophils and is entrapped, but not killed by NETs. The amount of NETs reduces over time due to the expression of nuclease A (SsnA), indicating that SsnA is a specific NET evasion factor in *S. suis* (116). In this sense, NET degradation is mediated not only by the known secreted SsnA but also by a putative endonuclease A of *S. suis* that is homologous to pneumococcal

TABLE 2 Lists the molecules for degradation of NET release in bacterial infections.

Evasion strategy	Molecule (s)	Microorganism	Modulatory effect on NETs formation	References
Degradation	Nuc	<i>S. aureus</i>	Escaping from NET-mediated killing and facilitates increased survival of <i>S. aureus</i>	(101, 102)
	Eap		Aggregate extracellular DNA and protecting the bacteria from NETs	(103, 104)
	Ads		Conversion of NETs to deoxyadenosine, which triggers-mediated death of immune cells	(105, 106)
	ArlRS-MgrA		Control NET-evasion mechanisms and regulate nuclease expression that involved in degradation of NETs	(107)
	ComK		Upregulate glucose and DNA-uptake and downregulate ROS production	(108)
	FnBPB		Bind to histone H3 and plasminogen, and cleave the bound histone	(109)
	EddB	<i>P. aeruginosa</i>	Degrade extracellular DNA to defend against NETs	(110)
	EddA		Removing the cation-chelating phosphates from the extracellular DNA phosphodiester backbone	(110)
	PAD4		Citrullination of extracellular histone H3.1	(111)
	Sda1	GAS	Enables bacteria to evade the host immune response by degrading the DNA backbone of NETs	(77, 112)
	SpnA			(113)
	endA	<i>S. pneumoniae</i>	Allows pneumococci to degrade the DNA scaffold of NETs	(76, 114)
	TatD			(115)
	SsnA	<i>S. suis</i>	They favor for the degradation of NETs	(116)
	endA			(117)
	ApdS			Cleave cathelicidin LL-37, impairs its ability to promote NETs formation and ROS production
	SWAN	<i>S. sanguinis</i>	Contributes to escape and degradation of NETs	(119)
	Thermonuclease	<i>N. gonorrhoeae</i>	Enables bacterium to escape from NET-mediated trapping and killing	(120)
	Nuc	<i>Y. enterocolitica</i>	Acts as Ca ²⁺ /Mg ²⁺ -dependent NET-degrading enzyme	(121)
	Dns and Xds	<i>V. cholera</i>	Degrade the DNA of NETs via the combined activity of the two extracellular nucleases	(122)
	Nuc	<i>Leptospira</i> spp.	Enable to degrade the NET structure	(123)
	LAV		Involved in modulation of NET defense through their nuclease activity	(124)
	Surface-lipoproteins		Assess in innate immune modulation and showed their nuclease activity	(125)
	NucA and NucD	<i>P. intermedia</i>	Able to degrade the DNA matrix comprising NETs	(126)
	Nuc	<i>A. hydrophila</i>	Use their nuclease to degrade NETs	(127)
	Nuc MAP3916c	<i>M. avium</i> subsp. <i>paratuberculosis</i>	Relevant to NETs degradation	(128)
	MnuA	<i>M. bovis</i>	A major membrane nuclease is rapidly degrade NETs, and play a significant role in virulence	(129)
	MbovNase		Secretory and membrane protein with ability to degrade NETs and induce apoptosis	(130)
	Mpn491	<i>M. pneumoniae</i>	Play a critical role in degradation of NETs	(131)
	Mhp597	<i>M. hypopneumoniae</i>	Involve in cytotoxicity, inflammation and degradation of NETs	(132)
Nuc	<i>M. hominis</i>	Promoting degradation of NETs	(133)	
PAD4	<i>P. gingivalis</i>	Citrullinate the histone H3, and promoting the bacterial escape from NETs	(134)	

(Continued)

TABLE 2 Continued

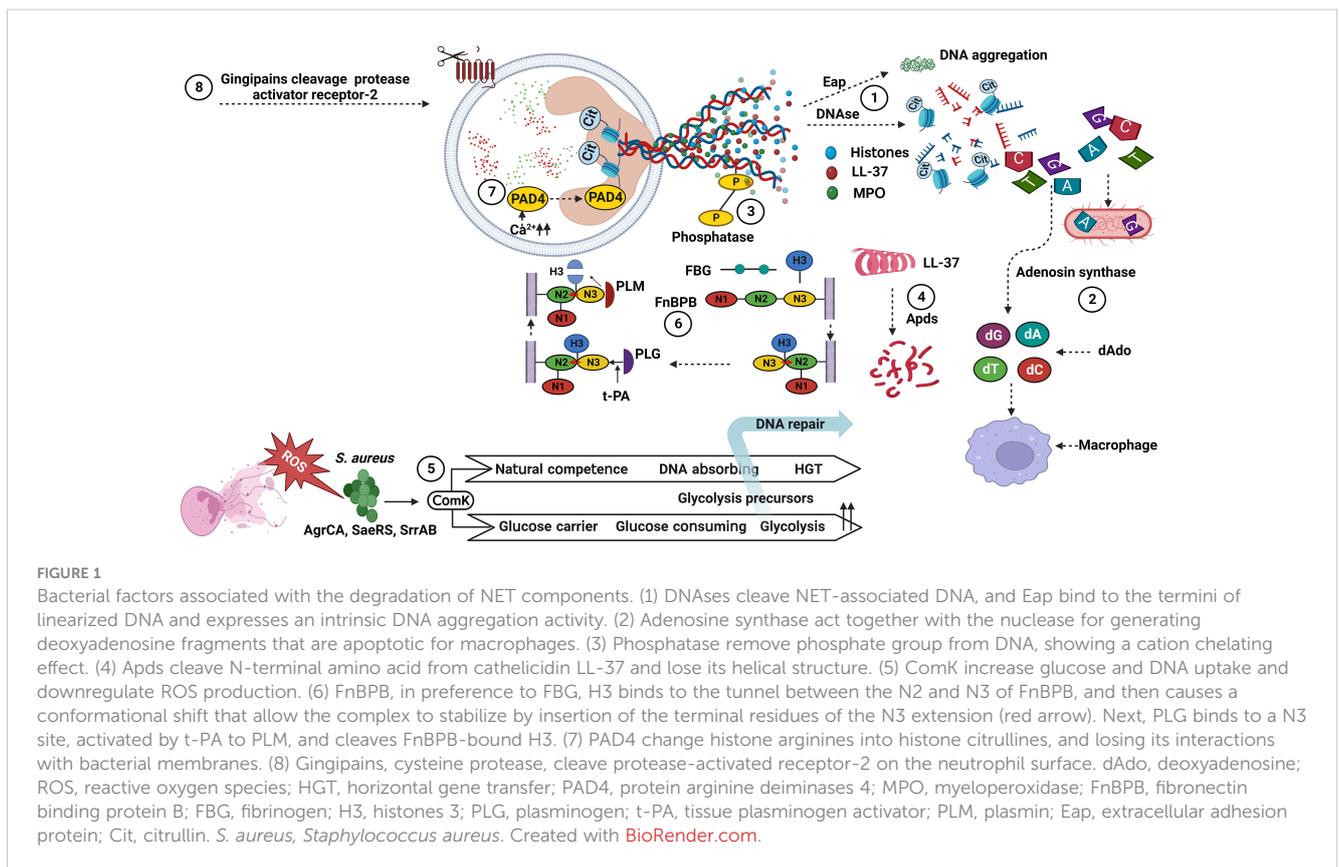
Evasion strategy	Molecule (s)	Microorganism	Modulatory effect on NETs formation	References
	Gingipains		Cleavage of protease activated receptor on the neutrophil surface and prevent <i>P. gingivalis</i> from NETs entrapment	(51)
	?	<i>K. pneumoniae</i>	Affecting the mobilization of the primary granules that necessary for NETs formation	(135)

S. aureus, *Staphylococcus aureus*; *P. aeruginosa*, *Pseudomonas aeruginosa*; GAS, group A *Streptococcus*; *S. pneumoniae*; *Streptococcus pneumoniae*; *S. suis*, *Streptococcus suis*; *S. sanguinis*, *Streptococcus sanguinis*; *N. gonorrhoeae*, *Neisseria gonorrhoeae*; *Y. enterocolitica*; *Yersinia enterocolitica*; *V. cholera*, *Vibrio cholera*; *P. intermedia*; *Prevotella intermedia*; *M. bovis*, *Mycoplasma bovis*; *M. pneumoniae*, *Mycoplasma pneumoniae*; *M. hypopneumoniae*, *Mycoplasma hypopneumoniae*; *M. hominis*, *Mycoplasma hominis*; *P. gingivalis*, *Porphyromonas gingivalis*; *K. pneumoniae*, *Klebsiella pneumoniae*; Nuc, nuclease; Eap, extracellular adhesion protein; Ads, adenosine synthase; FnBPB, fibronectin-binding protein B; EddB, extracellular DNA degradation protein B; EddA, extracellular DNA degradation protein A; PAD4, protein arginine deiminase 4; SpnA, *Streptococcus pyogenes* nuclease A; EndA, endonuclease A; SsnA, *Streptococcus suis* nuclease A; SWAN, streptococcal wall-anchored nuclease; LAV, variable region of *Leptospira* immunoglobulin-like protein A; MnuA, membrane nuclease A; MbovNase, *Mycoplasma bovis* nuclease; Mpn491, *Mycoplasma pneumoniae* nuclease 491; Mhp597, *Mycoplasma hypopneumoniae* 597; ?, unknown.

EndA (117). *Actinobacillus pleuropneumoniae* does not produce its own NET-degrading nucleases, but is hijacking other nucleases from host or from other co-infecting bacteria such as *S. suis* as a source for nicotinamide adenine dinucleotide (NAD) needed for efficient growth in the presence of NETs (137).

Moreover, *Streptococcus sanguinis* utilizes cell surface nuclease with a cell-wall anchor domain, termed streptococcal wall-anchored nuclease (SWAN), and contributes to bacterial resistance against the bactericidal activity of NETs (119). *Neisseria gonorrhoeae* encodes a putatively secreted thermonuclease that is implicated in biofilm remodeling and degrades the NET matrix to help *N. gonorrhoeae* from killing by neutrophils (120).

Yersinia enterocolitica O:3, O:8 and O:9 are able to induce NETs in human blood-derived neutrophils, but the amount of NETs is reduced at a later time, suggesting that the degradation of NETs has occurred and postulates that *Y. enterocolitica* produces Ca^{2+}/Mg^{2+} -dependent NET-degrading nuclease (121). *Vibrio cholerae* induces the formation of NETs upon contact with neutrophils, while *V. cholerae* in return to expresses two extracellular nucleases, Dns and Xds, in the presence of NETs, and rapidly degrades the DNA component of the NETs by the combined activity of the two nucleases (122). *Leptospira* spp. is able to induce NETs using human *ex vivo* and murine *in vivo* models, resulting in the release of NETs. However, *Leptospira* spp. exerts nuclease activity and



degrades DNA, resulting in a significantly reduced amount of NETs (123). In addition, the domain of the variable region of *Leptospira* immunoglobulin-like protein A (LAV) is involved in immune modulation; LAV has a nuclease activity and is demonstrated in the evasion of *Leptospira* from NETs (124). Additionally, surface-exposed lipoproteins in *Leptospira* are important for modulating host immune responses, and most of Len family surface proteins exhibit nuclease activity and are linked to NETs degradation (125).

Oral periodontopathogenic *Prevotella intermedia* produces two nucleases, NucA and NucD, which require Mg^{2+} and Ca^{2+} for their nuclease activity and contribute to NETs degradation (126). The fish pathogen *Aeromonas hydrophila* combats NETs using nuclease activity, while treatment of cells with β -glucan significantly protects NETs against bacterial degradation (127). *Mycobacterium avium* subsp. *paratuberculosis* encodes an extracellular nonspecific DNase that can destroy the NETs and promotes bacterial survival *in vitro* and *in vivo* (128).

Mycoplasma are the smallest bacteria that can infect and cause serious disorders in humans and various animal species (138, 139). Nucleases are a crucial component of *Mycoplasma* pathogenesis, facilitating bacterial growth and persistence in the host by digesting host nucleic acids and producing free nucleotide precursors (140–142). Membrane-associated or secreted nucleases have been found in many *Mycoplasma* species (129, 132, 143–146), and are homologous to staphylococcal nuclease (101). *Mycoplasma* lipoproteins are a major determinants of NET release during the innate immune response (39). Interestingly, most of the described *Mycoplasma* nucleases are able to escape from NET entrapment and killing by digesting NET's DNA backbone, reducing structure stability, and enhancing NET elimination (129–131, 133).

4.2.2 PAD4 secretion

Although DNA has been thoroughly examined, it is not the only NET component that is susceptible to degradation. PAD4 capable of deaminating arginine to citrulline and has been linked to NET formation in various context (147). PAD4 is involved in NET-mediated bacterial trapping and killing. Histones with cationic residues interact with negatively charged bacterial membranes and disrupt them (148). Thus, the loss of the positive charge of histones can lower their antibacterial function due to PAD4 activity. For example, *Porphyromonas gingivalis* produces its own PAD, *Porphyromonas* peptidylarginine deiminase (PPAD), which citrullinates histone H3, thereby facilitating bacterial escape from NETs, whereas PAD-mutant *P. gingivalis* is more prone to NET-mediated killing than its wild-type counterpart (134). Moreover, histone 3.1 displays bactericidal activity against *P. aeruginosa*. This bactericidal effect is reduced following citrullination by PAD4 or proteolysis by NE (111).

4.2.3 Degradation of NET-bound proteins

As previously mentioned, host defense peptides are key components of the innate immune system and act as the principal first line of defense against invading pathogens (149). The cysteine protease ApdS from *S. suis* cleaves cathelicidin LL-37 and impairs its ability to promote NETs formation and ROS

production (118). *K. pneumoniae* affects the mobilization of primary granules and their components, which harbor proteins with more potent bactericidal properties and those related to NETs (135). Gingipain is a cysteine protease responsible for the virulence of *P. gingivalis* and is dependent on proteolytic activation of protease-activated receptor-2 (PAR-2). Intriguingly, *P. gingivalis* and purified Arg-specific gingipains (Rgp) induce NETs that not only lack bactericidal activity, but also stimulate the growth of bacterial species otherwise susceptible to killing in NETs. Taken together, gingipains play a dual role in NETs; they are potent direct inducers of NETs formation; however, their activity prevents *P. gingivalis* entrapment and subsequent killing (51). *S. aureus* produces a cell-wall-anchored protein known as fibronectin-binding protein B (FnBPB) that is the main histone receptor and bind to all types of histones. FnBPB provides a dual immune-evasion function that captures histones, and prevents them from reaching the bacterial membrane, and simultaneously binds plasminogen, thereby promoting its conversion to plasmin to destroy the bound histone (109).

4.3 NET resistance mechanisms

In addition to inhibition of NET release and the degradation of NETs components, certain bacteria are resistant to the antimicrobial activity of NETs (Table 3).

4.3.1 Capsule

Capsule is a surface structure of the organism and plays a critical role in virulence, principally by interfering with host clearance mechanisms. The thickness of the pneumococcal capsule plays a crucial role in determining the extent of NET formation and may contribute to pneumonia severity (161, 162). Interestingly, the electrostatic charge of the capsule helps evade NET-mediated killing by repelling interactions with antimicrobial proteins in the DNA framework. In this context, *S. pneumoniae* contains a *dlt* operon that mediates the incorporation of d-alanine residues into lipoteichoic acid (LTA), thereby introducing a positive charge that reduces trapping by NETs *in vitro* (150). *Kingella kingae* polysaccharide capsule and exopolysaccharide function distinctly to promote neutrophil evasion. The *K. kingae* polysaccharide capsule prevents ROS production and neutrophil association, whereas the *K. kingae* exopolysaccharide reduces neutrophil phagocytosis and sensitivity to antimicrobial peptides (152). In addition, the hyaluronic acid capsule and M protein of the GAS serotype MIT1 promote resistance to human cathelicidin LL-37, which may be an important contributor to the NET-resistance phenotype (155).

4.3.2 Biofilm formation

Microbial biofilm communities are microbes embedded in a matrix of self-produced polysaccharides and other molecules, such as lipids, proteins, and nucleic acids that can bind to various surfaces, which complicates the immunological and therapeutic response (163). Biofilm formation by *P. aeruginosa* is a major

TABLE 3 Molecules involved in the resistance of NET components in bacterial infections.

Evasion strategy	Molecule (s)	Microorganism	Modulatory effect on NETs formation	References
Resistance	D-alanylated LTA	<i>S. pneumoniae</i>	Mediates the incorporation of d-alanine residues into LTA, introducing positive charge, and reduces NETs trapping	(150)
	Biofilm		Provide resistance to NET-mediated killing	(151)
	Lipid A of LPS	<i>N. meningitidis</i>	Phosphoethanolamine modification of LPS interfere with the action of NET-bound cathepsin G	(75)
	ZnuD		Essential for absorbing Zn ²⁺ and reduces the effects of nutritional immunity mediated by NETs	(75)
	OMVs		Suppressing adherence to NETs	(75)
	CPS	<i>K. kingae</i>	Protecting from ROS-mediated killing and antimicrobial peptides	(152)
	M1	GAS	Provides resistance to NETs-derived cathelicidin LL-37 by sequestering the cationic peptides	(15, 153)
			Provide resistance against NETs-mediated histones	(14)
	T4 pili	GAS M4	Sequester haptoglobin to confer M4 GAS resistance to antibacterial of LL-37 and CRAMP	(154)
	Hyaluronic acid capsule	GAS M1T1	Promote resistance to human cathelicidin LL-37 resistance and survival within NETs	(155)
	M protein		Inhibit NET-released MPO and protects GAS from antimicrobial peptides within the NETs	(156)
	Collagen-like protein-1			
	PVL and γ -hemolysin AB	<i>S. aureus</i>	Necessary for biofilm-mediated neutrophil killing	(12)
	LOS	NTHI	Initiate in the development of biofilm and mediate resistance to NET killing	(23, 157)
	Peroxiredoxin-glutaredoxin and catalase		Inhibit the oxidative burst in NETs	(158)
	Exopolysaccharide, T3SS	<i>P. aeruginosa</i>	Formation of biofilm and dead zone and display resistant to neutrophil killing	(71)
	Exopolysaccharide		Acquire resistance to NET-mediated killing in the CF airway	(74)
	OMVs		Inhibition adherence to NETs	(159)
Biofilm	<i>S. suis</i>	Inhibit the formation of NETs	(160)	

S. pneumoniae, *Streptococcus pneumoniae*; *N. meningitidis*, *Neisseria meningitidis*; *K. kingae*, *Kingella kingae*; GAS, group A *Streptococcus*; NTHI, nontypeable *Haemophilus influenzae*; *S. aureus*, *Staphylococcus aureus*; *Pseudomonas aeruginosa*, *P. aeruginosa*; *S. suis*, *Streptococcus suis*; LTA, lipoteichoic acid; LPS, lipopolysaccharide; OMVs, outer membrane vesicles; CPS, capsular polysaccharide; PVL, Pantone Valentine leukocidin; CRAMP, cathelicidin-related antimicrobial peptide; LOS, lipooligosaccharide; MPO, myeloperoxidase; T3SS, type 3 protein secretion system.

cause of bacterial keratitis and is facilitated by bacterial Psl exopolysaccharide and T3SS. NETs are stimulated by high expression of T3SS and form a barrier, known as dead-zone, confining bacteria to the external corneal environment, preventing them from spreading to the brain. Once formed, ocular biofilms advance eye pathology because they are resistant to neutrophil killing and antibiotics (71). Furthermore, *P. aeruginosa* acquires resistance to NET-mediated killing in cystic fibrosis airways. This resistance correlates with the development of excess exopolysaccharide production (which characterizes the mucoid phenotype) (74). In addition, studies conducted *in vitro* have demonstrated that *P. aeruginosa* can profit from the released DNA of NETs and incorporate it into the extracellular matrix, potentially strengthening the matrix's resistance to antibiotics and host antimicrobial peptides (164–167).

Clinical isolates of *H. influenzae* share a common tendency to produce biofilms, and the factors that facilitate biofilm formation

include the expression of certain lipooligosaccharide (LOS) glycoforms (168–170), type IV pili (171), and double-stranded DNA release (172). Nontypeable *Haemophilus influenzae* (NTHi) promotes resistance to killing within NETs structures through LOS moieties that promote biofilm formation (23, 157). Methicillin-resistant *S. aureus* (MRSA) biofilms rapidly skew neutrophils toward NETs formation through the combined activity of the Pantone-Valentine leukocidin (PVL) and γ -hemolysin AB, which are important for biofilm-mediated neutrophil killing. Through this response, *S. aureus* can persist because the antimicrobial activity of the released NETs is ineffective in eradicating bacterial biofilm (12). *S. aureus* nuclease-mediated NET degradation promotes the persistence of biofilm bacteria entrapped in NETs (173). *S. suis* serotype 2 induces NETs release and can be captured by the NETs, whereas biofilm formation inhibit NETs release through the biofilm extracellular matrix and enables survival by allowing the pathogen to persist and resist the host immune system (160). In addition,

pneumococci produce biofilms *in vivo* and observe web- or net-like structures surrounded by dense matrix material, which is intertwined with the formation of NETs (151).

4.3.3 Outer membrane vesicles

OMVs are nanostructures released by pathogenic and non-pathogenic bacteria *in vivo* and *in vitro* and can act as decoys for NET capture (174). Ocular keratitis is often associated with *P. aeruginosa* infection. Neutrophils release NETs in response to both cytotoxic and invasive clinical isolates of *P. aeruginosa*. Cytotoxic strains are less prone to NET capture than invasive strains because they release OMVs that inhibit NET adherence (159). Furthermore, *Neisseria meningitidis* releases OMVs as potent NET inducers. NETs are unable to kill NET-bound meningococci, but they slow down their proliferation rate. The bacteriostatic effect of NETs is counteracted by spontaneously released OMVs from *N. meningitidis*, which reduces their adherence to NETs (75).

4.3.4 Charge surface alteration

NET-releasing proteins attach to negatively charged phospholipids in pathogen membranes with electrostatic affinity, which promotes death (175). Nonetheless, certain bacteria modify their cell surfaces, which reduces their affinity for attachment to NET-releasing peptides. For example, the surface-associated protein M1 protein contributes to GAS virulence by interfering with NET-mediated killing, which sequester and neutralize cathelicidin LL-37 through the N-terminal hypervariable (HV) region and A repeat region that encode the type-specific immunologic epitopes of the M1 serotype (15, 153). In addition, the N-terminal portion of the M1 protein binds and inactivates histones before they reach their cell wall target of action and mediate resistance against released extracellular histones in NETs, allowing the pathogen to tolerate high concentrations of histones and promote survival in NETs (14). Streptococcal collagen-like protein 1 (Scl-1) in GAS serotype MIT1 confers resistance to NET-mediated killing, which may be in large part due to the antimicrobial peptides present within the NETs; Scl-1 has an additional role in suppressing the release of MPO, which ultimately limits the production of NETs (156). Haptoglobin is an abundant acute-phase protein produced upon infection, which binds to human neutrophils and monocytes and inhibits their functions (176, 177). The T4 antigen, the pilus backbone protein of GAS M4, sequester the host haptoglobin. Coating M4 GAS with haptoglobin causes a reduction in susceptibility to cathelicidin LL-37 and murine cathelicidin-related antimicrobial peptide (CRAMP) and promotes resistance to NET-mediated killing (154).

Modification of lipid A of meningococcal LPS with phosphoethanolamine shields *N. meningitidis* from the action of NET-bound cathepsin G (75). In a process known as nutritional immunity, host organisms restrict the availability of trace nutrients in the blood or secretions to prevent the growth of invading microorganisms (178). The outer membrane receptor ZnuD of *N. meningitidis* is crucial for Zn²⁺ uptake at very low concentrations (179). *N. meningitidis* utilizes high affinity absorption systems for critical ions on mucosal surfaces, producing ZnuD, which absorbs Zn²⁺; contribute to survival within NETs (75).

4.3.5 Antioxidant enzymes secretion

Finally, the initiation of the oxidative burst is important for the induction of NETs, and oxidants contribute to microbicidal activity within the NETs (9, 180). Noticeable *H. influenzae* expresses the bifunctional peroxiredoxin-glutaredoxin (encoded by *pdgX*) and catalase (encoded by *hktE*), which confer resistance of NTHI to oxidative killing and thus promote the survival of NTHI within NET structures and persistence *in vivo* in the lung and middle ear. In addition, exogenous catalase partially rescued NTHI from NET-mediated killing *in vitro*. The expression of both peroxiredoxin-glutaredoxin and catalase is a mechanism by which NTHI combats the effects of NETs (158).

5 Concluding remarks

Neutrophils are type of white blood cell that play a crucial role in the immune system's defense against infections. There are different subsets of neutrophils that have different functions and responses to various stimuli. NET release is a form of neutrophil immune response that, depending on the context in which it is examined, can have both pathogenic and physiological effects. They can entangle and immobilize bacteria, preventing their spread, and facilitating their destruction by other immune cells. Additionally, dysregulation of NET release has several implications for the immune system and overall health. On the other hand, impaired NET formation may lead to reduced ability to fight off infections. Therefore, maintaining a balanced and controlled NET release is essential for the proper functioning of the defense system and overall health. In recent years, there has been a significant increase in research focused on the role NETs in response to pathogens and the mechanisms involved in the modulation of their release. Bacteria have developed various mechanisms to evade or resist NET release, allowing them to escape the immune system's defenses and several key findings and advancements have emerged from these studies. In this review, we have discussed the strategies used by various bacteria to counteract NET-mediated antimicrobial effects as such inhibiting NET release, deactivating their components, degrading their net-like framework, or blocking their contact, resulting in infection dissemination and immune system inactivation. Bacteria possess a vast array of mechanism for modulating NET activity, and ongoing investigations are expected to uncover new molecules and pathways involved in controlling NET release. Current understanding of different inflammatory mediators in modulate NET release is quite limited and need be further elucidated. Overall, the recent focus on NETs and their modulation has provided a deeper understanding of the complex interplay between neutrophils, pathogens, and the immune system. This knowledge has the potential to identify pharmacological targets and drive the development of therapeutic and diagnostic approaches to counteract bacterial evasion strategies and combat the role of NETs in inflammatory and autoimmune diseases. It is crucial to understand that various factors affect whether NETs are advantageous or harmful, with the dose and the timing of NET release and clearance being critical factors. A better understanding

of the roles of NETs and their effects on hosts will make it possible to inhibit the adverse attributes without affecting the beneficial ones, which will ultimately enable strategies related to NETs to be used in disease treatment.

Author contributions

AA: Investigation, Visualization, Writing – original draft. HH: Investigation, Visualization, Writing – review & editing. SLan: Investigation, Visualization, Writing – review & editing. ZL: Investigation, Visualization, Writing – review & editing. SLiu: Investigation, Visualization, Writing – review & editing. SC: Conceptualization, Funding acquisition, Investigation, Supervision, Visualization, Writing – review & editing. YC: Funding acquisition, Project administration, Supervision, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

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Glossary

ACT	Adenylate cyclase toxin
AdsA	Adenosine synthase A
C5a	Complement factor 5a
cAMP	Cyclic adenosine monophosphate
CLRs	C-type lectin receptors
ComK	Competence regulator
CPS-I	Capsular polysaccharide I
CRAMP	Cathelicidin-related antimicrobial peptide
CRs	Complement receptors
dAdo	Deoxyadenosine
Eap	Extracellular adherence protein
FnBPB	Fibronectin-binding protein B
GAS	Group A <i>Streptococcus</i>
GBS	Group B <i>Streptococcus</i>
GM-CSF	Granulocyte-macrophage colony-stimulating factor
HMW-HA	High-molecular-weight hyaluronic acid
IFN	Interferon
IL	Interleukin
LOS	Lipooligosaccharide
LPS	Lipopolysaccharide
LTA	Lipoteichoic acid
LTH	Leukotoxic hypercitrullination
MAPK	Mitogen-activated protein kinase
MPO	Myeloperoxidase
MRSA	Methicillin-resistant <i>S. aureus</i>
NE	Neutrophil elastase
NETs	Neutrophil extracellular traps
NLRs	Nucleotide-binding oligomerization domain-like receptors
NTHi	Nontypeable <i>Haemophilus influenzae</i>
Nuc	Nuclease
OMVs	Outer membrane vesicles
PAD4	Protein arginine deiminase 4
PAR-2	Protease activated receptor-2
PVL	Panton-Valentine leukocidin
ROS	Reactive oxygen species
Scl-1	Streptococcal collagen-like protein 1
Siglec-5	Sialic acid-binding Ig-like lectin-5
Siglec-9	Sialic acid-binding Ig-like lectin-9

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SLO	Streptolysin O toxin
SWAN	Streptococcal wall-anchored nuclease
T3SS	Type 3 protein secretion system
TGF	Transforming growth factor
TLRs	Toll-like receptors
TNF	Tumor necrosis factor
Wip1	Wild-type p53-induced phosphatase 1