Microbiological Research 243 (2021) 126644

Contents lists available at ScienceDirect

Microbiological Research

journal homepage: www.elsevier.com/locate/micres

Avoiding the trap: Mechanisms developed by pathogens to escape neutrophil extracellular traps

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ARTICLE INFO

Keywords:
Neutrophil extracellular traps
Pathogens
Degradation
Evasion
Inhibition

ABSTRACT

Neutrophils are the first cells of the innate immune system that respond to infection by arriving at sites when pathogens have exceeded physical barriers. Among their response mechanisms against pathogens is the release of neutrophil extracellular traps (NETs), which are composed of deoxyribonucleic acid and antimicrobial proteins such as neutrophil elastase, myeloperoxidase, antimicrobial peptides, and other proteins in neutrophil granules. The formation of extracellular traps is considered an effective strategy to capture and, in some cases, neutralize pathogenic bacteria, fungi, parasites, or viruses. However, it is also known that pathogens can respond to NETs by expressing some virulence factors, thus evading the antimicrobial effect of these structures. These include the secretion of proteins to degrade the deoxyribonucleic acid scaffold, the formation of biofilms that impede the effect of NETs, or the modification of its membrane structure to avoid interaction with NETs. In this review, we discuss these mechanisms and summarize the different pathogens that employ one or more mechanisms to evade the NET-mediated neutrophil response.

1. Introduction

Neutrophils are the most abundant cells of the immune system and the first to reach infection sites, performing an essential role in the innate immune response against multiple pathogens (Papayannopoulos and Zychlinsky, 2009; Papayannopoulos, 2017). After a maturation process in the bone marrow, neutrophils are released into the circulatory system, where they respond to inflammatory signals by migrating to the site of infection in a process regulated and controlled by chemokines, passing through the epithelium to eliminate pathogenic microorganisms (Amulic et al., 2012; Cooper et al., 2013).

Neutrophils eliminate microorganisms by phagocytosis, degranulation, or by the release of neutrophil extracellular traps (NETs) (Fuchs et al., 2007). NETs are mainly composed of decondensed chromatin mixed with granular and cytoplasmic proteins. Its release allows the capture and elimination of microorganisms by the action of antimicrobial peptides contained in the deoxyribonucleic acid (DNA) network (Cooper et al., 2013). The mechanism for NETs formation is not fully understood, however, it is known that, in some cases, the nicotinamide adenine dinucleotide phosphate (NADPH) oxidase pathway may participate depending on the stimulus, and that granular molecules, such as the neutrophil elastase and myeloperoxidase, are necessary for their formation (Amulic et al., 2012).

Multiple stimuli promote the release of NETs. These include the interaction of the neutrophil with other immune system cells (platelets) after activation with cytokines (IL-8) that help to quickly contain and eliminate pathogens (Clark et al., 2007). Additionally, NETs release also has been observed in response to whole microorganisms or their proteins, such as Gram-positive and Gram-negative bacteria, as well as yeast, parasites, and virus (Branzk et al., 2014; Brinkmann, 2018; Kenny et al., 2017). However, the formation of these structures has been characterized to happen in a lytic or vital way, in the first the neutrophil dye to extrude their DNA whereas in the least the neutrophil extrudes its DNA but can continue with other antimicrobial activities such phagocytosis (Hoppenbrouwers et al., 2017).

It has also been observed that different pathogens have developed mechanisms to counteract the antimicrobial effects of neutrophils, either by preventing their capture, neutralizing the effect of antimicrobial proteins, or by inhibition or degradation of NETs. Even though several mechanisms for survival against NETs carried out by pathogens have already been described, there are still many mechanisms that are not fully described. In this review, we first describe the process of

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https://doi.org/10.1016/j.micres.2020.126644
Received 10 August 2020; Received in revised form 28 October 2020; Accepted 1 November 2020
Available online 5 November 2020

formation of NETs, and then we review some mechanisms used by pathogens to evade the formation and activity of these structures such as nuclease expression, polysaccharide capsule, biofilm formation, cell surface modification; finally, we discuss the specific mechanisms described to suppress or inhibit NETs formation.

2. Neutrophil extracellular traps

NETs formation is a process called NETosis, which is characterized as a type of cell death with cell changes that are different from those described for apoptosis and necrosis, as there is no DNA fragmentation in neutrophils, but a disintegration of the nuclear and internal membrane that promotes a mixture of nuclear and cytoplasmic contents; in addition, this type of death does not depend on caspase activity (Fuchs et al., 2007). NETs are fibrous structures composed of decondensed chromatin mixed with around 30 different proteins (e.g., neutrophil elastase [NE], myeloperoxidase [MPO], cathelicidin, lactoferrin, gelatinase), which allow neutrophils to capture, neutralize and eliminate pathogenic microorganisms (Branzk and Papayannopoulos, 2013). During the formation of these structures, the neutrophil undergoes important changes leading to the release of decondensed chromatin in the extracellular medium (Fig. 1). This process begins with the loss of differentiation between euchromatin and heterochromatin producing delobulation of the nucleus; later, the nuclear membrane begins to separate to complete disintegration. Subsequently, the membrane of the granular vesicles is also dissociated, allowing the cytoplasm, nuclear, and granular components to mix. Finally, the cell membrane breaks, and the components are released into the extracellular medium (Fuchs et al., 2007).

This process can occur in two distinct ways: the first involves a lytic or suicidal mechanism, which usually occurs slowly (2−4 h) and involves the rupture of the neutrophil plasma membrane. The second does not involve cell death and is named vital netosis. In this process, within minutes, the neutrophil releases its contents to the extracellular space through vesicles, while it is still capable of carrying out its phagocytic and degranulation functions (Yipp and Kubes, 2013; Jorch and Kubes, 2017). The type of stimulus detected by the neutrophil for NETs formation is essential, as it determines the release mechanism that will take place. The stimulation of neutrophils with phorbol-12-myristate-13-acetate (PMA) has been reported to promote a lytic NETosis. During this, the protein kinase C (PKC) pathway is activated, promoting the generation of oxygen free radicals (reactive oxygen species [ROS]) through the activity of the NADPH oxidase complex; as a general feature, this process takes more than three hours. Neutrophils have been also reported to induce vital NETosis in a very short time (i.e. five minutes to an hour) when exposed either *in vitro* or *in vivo* to microorganisms (e.g. *Staphylococcus aureus, Salmonella enterica*, *Shigella flexneri*, *Streptococcus pneumoniae*, *Candida albicans*); to bacterial derived molecules such as lipopolysaccharide (LPS); or specific cytokines such as interleukin 8 (IL-8) (Parker et al., 2012; Yipp et al., 2012; Gray et al., 2013; Pieterse et al., 2016; Hoppenbrouwers et al., 2017; Lauková and Konečná, 2018). Likewise, it has been suggested that neutrophil receptors can promote the formation of vital NETs by rapidly recognizing molecules associated with inflammatory processes, while the time it takes to permeate the cell membrane to PMA may be important in the formation of lytic NETs (Masuda et al., 2016; Yang et al., 2016; Gonzalez-Aparicio and Alfaro, 2019).

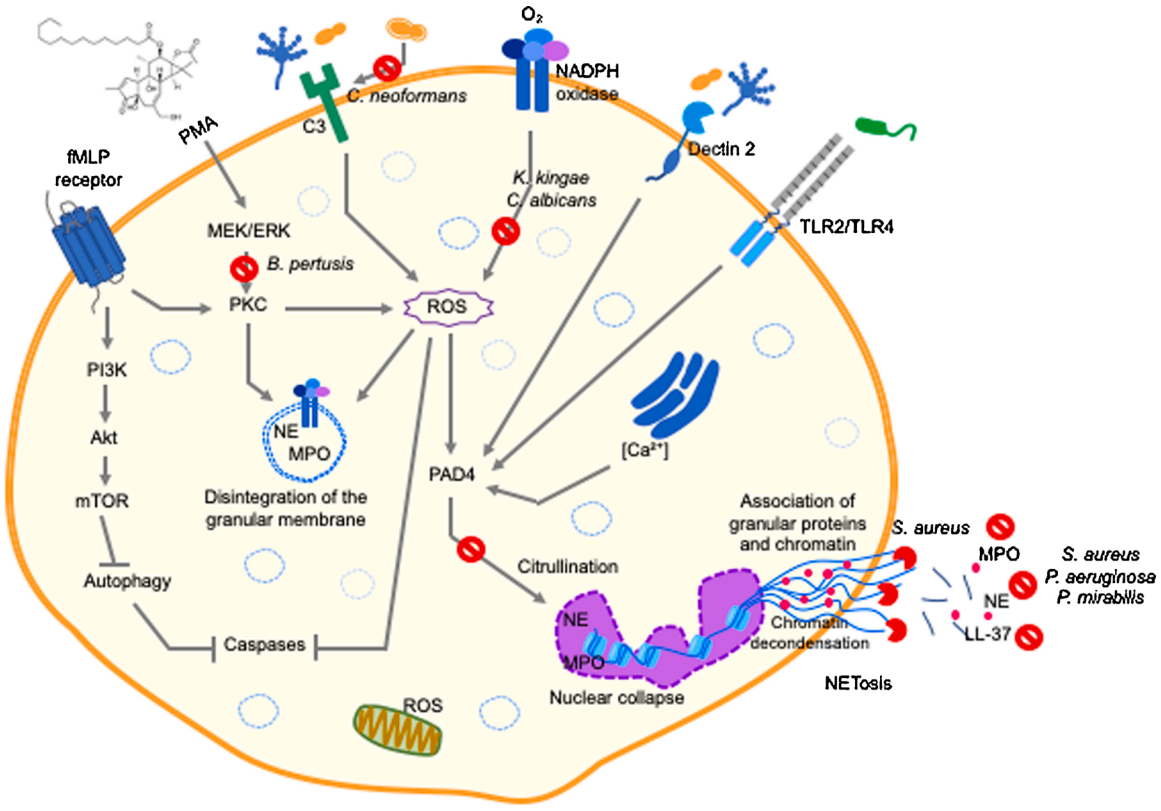

Fig. 1. General signaling pathways involved in the formation of neutrophil extracellular traps (NETs). The signaling pathways for NETs formation activated by different stimuli are shown. Additionally, pathways inhibited by pathogens to avoid recognition, inhibition of proteins activity, DNA cleavage, or NETs formation are also shown. Some examples of microorganisms that prevent NETs formation by inhibiting its recognition by neutrophil receptors, preventing activation of signaling pathways involved in the formation of NETs, or by degrading the extruded DNA through nuclease activity are depicted. NE: Neutrophil elastase, MPO: Myeloperoxidase, PMA: Phorbol-12-myristate-13-acetate, NADPH: Nicotinamide adenine dinucleotide phosphate, fMLP: N-formyl-methionyl-leucyl-phenylalanine, PI3K: phosphatidylinositol-3-kinase, Akt: serine/threonine protein kinase, ROS: reactive oxygen species, PAD4: protein arginine deiminase 4, TLR: Toll-like receptor.

3. Evasion of neutrophil extracellular traps

Although the formation of extracellular traps by neutrophils makes it possible to contain pathogens and prevent their spread, some bacteria (e.g. *S. aureus*, *S. pneumoniae*), fungi (e.g. *Aspergillus* spp., *C. albicans*), and parasites (e.g., *Plasmodium falciparum*, *Toxoplasma gondii*) have developed strategies that allow them to resist their capture or elimination by these structures (von Köckritz-Blickwede and Nizet, 2009; Arazna et al., 2013). Furthermore, it has been shown that some pathogens are even capable of modifying NETs to use them as a source of nutrients, or to avoid their recognition by other cells of the immune system capable of mediating its elimination (Seper et al., 2013). Among mechanisms utilized by microorganisms to evade NETs, are the promotion of their degradation, increased pathogen resistance by inducing modifications in their surface structures, or the suppression/inhibition of NETs formation. We discuss these in detail below and they are outlined in Table 1 and Fig. 1.

4. Nuclease expression

Nucleases are enzymes classified in the group of hydrolases, which are responsible for cleaving a phosphodiester bond between the pentose of one nucleotide and the phosphate group of another within nucleic acids. They can be further classified as endonucleases and exonucleases, in which the former cleaves the bond within a nucleotide chain, and the latter at the ends of the chain (Arazna et al., 2013). These microbial enzymes contribute to the replication or repair of genetic material; however, some pathogens produce extracellular nucleases as a strategy to escape elimination by NETs, allowing them to spread to other sites on the host (Doke et al., 2017; Nel et al., 2016). In line with this, Group A *Streptococcus* including *S. pyogenes*, *S. pneumoniae,* and *Streptococcus suis* serotype 2 which secrete Sda1, EndA, and SsnA nucleases respectively, promote NETs degradation allowing their dissemination (Buchanan et al., 2006; de Buhr et al. 2014). NETs elimination by *Yersinia enterocolitica* is avoided due to the activity of a nuclease requiring the presence of Ca^{2+} and Mg^{2+} as cofactors (Möllerherm et al., 2015); similarly, *Mycoplasma pneumoniae* uses Mg^{2+}-dependent nuclease Mpn491 to escape its elimination by NETs, and thus survive in the host (Yamamoto et al., 2017). *Neisseria gonorrhoeae* also expresses a Ca^{2+}-dependent thermonuclease denominated Nuc, that is required to degrade NETs, giving bacteria survival advantages (Juneau et al. 2015). Likewise, despite stimulating the release of NETs, *Mycoplasma bovis* is capable of rapidly degrading these structures *in vitro* through the expression of the membrane nuclease MnuA, which is critical for the survival of the bacteria, as mutants are unable to prevent their elimination by NETs if MNuA function is suppressed (Mitiku et al., 2018).

Of particular interest is that some pathogens promote the formation of NETs and subsequently, by nuclease activity, degrade the DNA scaffold and use the released phosphate groups for nutrition. *S. aureus* secretes a nuclease (Nuc), which digests the DNA of NETs, generating 5′and 3′ nucleotide monophosphates, which later, due to the activity of an adenosine synthase A (AdsA), also produced by this bacterium, are converted into deoxyadenosine (dAdo), a toxic component with the ability to trigger caspase-3-associated death in immune cells (Winstel et al., 2019). Similarly, *Vibrio cholerae* can evade its elimination by extracellular traps through two extracellular nucleases (Dns and Xds), which act synergistically to degrade NETs and promote the release of phosphate residues from the DNA structure to the medium, which are used by bacteria for their nutrition and proliferation (Seper et al., 2013).

Furthermore, some parasites can also express nucleases to avoid NETs. *Leishmania infantum* promastigotes can evade their elimination through the activity of the enzyme nucleotidase/nuclease 3′ (Guimarães-Costa et al., 2014).

5. Resistance to NETs

5.1. Polysaccharide capsule

The capsule is a virulence factor present in some microorganisms that allows them to avoid phagocytosis by immune cells, and therefore, their elimination. Structurally, it consists of approximately 98 different types of polysaccharides; is linked by covalent bonds to the peptidoglycan of the cell wall of microorganisms, and measure 400 nm thick. Simple capsular shapes found in bacteria consist of linear polymers of two or more monosaccharides, while the complex ones contain repeating unit branches of one to six monosaccharides with additional side chains (Paton and Trappetti, 2019). In fungi such as *Cryptococcus neoformans* and *C. gattii*, 90 % of the capsule is composed of glucuronoxymannan, the rest 10 % corresponds to galactans, and mannoproteins (Casadevall et al., 2019).

Composition, thickness, and physical properties of the capsule participate in the evasion of pathogens upon capture in NETs (Fig. 1 and Table 1) (Arazna et al., 2013). In *C. neoformans*, *capsule* components such Glucuronoxylmannan is essential for the inhibition of NETs *in vitro*, since mutations modifying this polysaccharide allow the recognition of this pathogen by neutrophils and the generation of NETs (Rocha et al., 2015). Likewise, capsule thickness also captures and eliminates pathogens by NETs, since the serotypes that have thicker capsules also have greater resistance to capture and elimination by extracellular traps (Moorthy et al., 2016). An electrostatic charge of the capsule is another strategy for evasion of NETs-mediated elimination since the cationic or neutral nature of the capsule is capable of repelling the interaction with the antimicrobial proteins contained in the DNA framework (Wartha et al., 2007). Likewise, the capsular components of some pathogens are capable of inhibiting important pathways for the formation of NETs. It is known that the polysaccharide capsule of *Kingella kingae* is capable of preventing the production of ROS, as well as the activation of the protein arginine deiminase 4 (PAD4) whose activity is essential for some forms of NETosis; in addition to conferring resistance to the activity of antimicrobial molecules, promoting bacterial survival and favoring infection (Muñoz et al., 2019).

Other components of the bacterial capsule also can contend with extracellular traps, such as the hyaluronic acid that envelops the surface of *Streptococcus* Group A serotype M1T1, which prevents its capture in NETs, in addition to conferring resistance to cathelicidin, one of the main components of these structures (Cole et al., 2010).

5.2. Biofilm formation

Biofilms are microbial communities embedded in a matrix of self-produced polysaccharides, as well as other molecules, such as lipids, proteins, and nucleic acids, that can bind to different surfaces. The association of microorganisms in biofilm communities can be triggered by specific signals in the environment, such as nutrient availability, temperature, or oxygen. Its formation follows a series of steps: first, there is an initial reversible union of planktonic cells; then, an irreversible union to the surfaces occurs; later, there is early maturation of the biofilm; and finally, produced polymeric substances allow the close association between organisms, and when environmental conditions become favorable, there is a dispersal of some organisms to return to the planktonic state (Van Houdt and Michiels, 2005). Biofilms play a fundamental role in various infections, since the organisms that compose it show greater resistance to various antibiotics, a reduced growth rate, and the ease of gene transfer, and the evasion of the response of the immune system due to the polysaccharide matrix (Gupta et al., 2016; Hong et al., 2009).

Polysaccharides of biofilms can vary depending on constituent microorganisms. Molecules such as alginate are present in the biofilm matrix of *Pseudomonas aeruginosa* together with its exopolysaccharides Pel (glucose-rich) and Psl (rich in mannose and galactose), whereas in yeasts biofilms, branched mannans associated with β-1,6 glucans are

Table 1
Mechanisms to avoid NETosis. Examples of microorganisms and their mechanism of evasion of elimination mediated by NETs.

Evasion strategy	Molecule(s) or process involved	Microorganism	Mechanism	Effect	Reference
Degradation	NucA and NucD	*Prevotella intermedia*	a) Requires Mg^{2+} y Ca^{2+} for activity to DNA degradation from NETs; b) use extracellular DNA as a source of nutrients (phosphate, nitrogen, and carbon)	Increase virulence, survival, and bacterial infiltration in host	Doke et al., 2017
	Nuc	*Staphylococcus aureus*	a) Degrades DNA to nucleotide monophosphates, and then converts them to deoxyadenosine (dAdo) which is toxic to other immune cells; b) mitigates neutrophil recruitment.	dAdo triggers noninflammatory apoptosis in macrophages; furthermore, bacteria continue to replicate and escape phagocytic killing without alerting the immune system	Winstel, et al. 2019
	Sda1	Group A *Streptococcus*	a) Avoid TLR9 recognition; b) decreased production of the proinflammatory cytokines (IFN-α and TNF-α)	Prevents recognition by phagocytes, increasing the risk of bacterial proliferation to produce infections	Uchiyama et al., 2012; Goldmann et al., 2004
	SsnA	*Streptococcus suis* serotype 2	Degrades DNA structure to escape NETs	Promotes spreading to other sites of infection	de Buhr et al., 2014
	EndA	*Streptococcus pneumoniae*	Degrades DNA structure to escape NETs	Promotes the spread of bacteria from the upper airways to the lungs, and from the lungs into the bloodstream	Beiter et al., 2006
	Mpn491	*Mycoplasma pneumoniae*	Mg^{2+} dependent nuclease; degrades NETs DNA	Prevents bacterial elimination	Yamamoto et al., 2017
	MnuA	*Mycoplasma bovis*	Homologated to Mpn491, degrade NETs DNA	Evades host immune response	Mitiku et al., 2018
	Nuclease	*Yersinia enterocolitica*	Ca^{2+} and Mg^{2+} dependent nuclease activity degrades NETs DNA	Avoids recognition and destruction by immune cells permitting the establishment of the infection	Möllerherm et al., 2015
	Dns and Xds	*Vibrio cholerae*	a) Degradation of NETs b) Use of DNA as a nutrient source	Facilitates survival in the human host	Seper et al., 2013
	Nuc	*Neisseria gonorrhoeae*	Degrade NETs structure.	1. Virulence increases and contributes to survival inside and outside of neutrophils; 2. Contributes to host colonization, including biofilm dispersal	Juneau et al., 2015b
	3′Nucleotidase/ nuclease	*Leishmania infantum*	Degradation of NETs	Survival increase in host	Guimarães-Costa et al., 2014
	Capsule	*Cryptococcus neoformans*	The polysaccharide has poor immunogenic and immunomodulatory properties	Confers protection to neutrophils and other host immune cells	Casadevall et al., 2019
		Group A *Streptococcus* serotype M1T1	a) Avoids detection by neutrophil; b) Capsule promoted bacterial survival within NETs; c) confer resistance to cathelicidin	1. Promotes resistance to killing at the site of infection; 2. Promotes hypervirulence and invasive disease	Cole et al., 2010
Resistance	Biofilm	*Kingella kingae*	a) Avoids neutrophil activation; b) inhibits neutrophil binding to microorganisms; c) prevents ROS production	Promotes bacterial survival during infection	Muñoz et al., 2019
		Pseudomonas aeruginosa	a) Mucoid bacteria resist NETs; b) use DNA released from NETs incorporating it to the extracellular matrix	Increased tolerance to neutrophil antimicrobial peptides or antibiotics	Rybtke et al., 2015
		Candida albicans	a) Genes associated with polysaccharide matrix regulates resistance to NETs; b) prevent ROS production.	Inhibition of the host immune system	Johnson et al., 2016 Xie et al., 2012
		Candida glabrata	Polysaccharide matrix and manna-complex	1. Delays release of NETs; 2. Resists attack by phagocytes and allows it to form biofilms on mucosal surfaces and medical devices	Johnson et al., 2017
		S. suis serotype 2	Polysaccharide matrix	1. Increased resistance to host immune system and antimicrobials; 2. inhibit the effect of NETs	Ma et al., 2017
		Nontypeable *Haemophilus influenzae*	Lipooligosaccharides present in the mature biofilm matrix	1. Persistence during acute and chronic otitis media; 2. Increased resistance to immune clearance and antibiotic treatment; 3. Allows survival within NETs	Hong et al., 2009
		S. pneumoniae	Decreases bacterial elimination inside NETs	Promotes recurrent or persistent infections	Reid et al., 2009
	Cell membrane modification	Methicillin-resistant *S. aureus*	a) In their growth as a biofilm, they release leukocidins, such as PVL or HlgAB, which induce NETosis, which probably influence neutrophil elimination activity; b) Bacteria remain viable after exposure to neutrophils suggesting that *S. aureus* may prevent the bactericidal activity of NETs antimicrobial proteins	1. Evades the host innate immune system 2. Increases persistence in chronic infections and tolerance to antimicrobials	Bhattacharya et al., 2018
		S. aureus	Incorporates D-alanine into the membrane to reduce a negative charge, thereby limiting the interaction of cationic peptides	1. Increases protection against host defense peptides, antibiotics, and NETs components	Peschel et al., 1999
		Group A *Streptococcus*		1. Promotes evasion of mucosal defenses and produce systemic infection; 2.	Kristian et al., 2005

(*continued on next page*)

Table 1 (*continued*)

Evasion strategy	Molecule(s) or process involved	Microorganism	Mechanism	Effect	Reference
			Incorporates D-alanine binding to lipoteichoic acid, which increases the positive surface charge	Increases protection against NETs components	
		Salmonella enterica	Incorporates palmitate or 4-amino arabinose to lipid A by activation of the PmrA-PmrB two-component regulatory system, to reduce the negative charge on the membrane	1. Resistance to host innate system within intestinal tissues; 2. Increases bacterial survival within macrophages; 3. avoid the interaction of antimicrobial peptides	Gunn et al., 2000
		Listeria monocytogenes	D-alanylation of lipoteichoic acid	1. Increased virulence; 2. increases resistance to cationic peptides of NETs	Abachin et al., 2002
		S. aureus	MprF protein synthesizes lysyl-phosphatidylglycerol, which alters the electrostatic properties of the membrane, a positively charged phospholipid	1. Contributes to bacterial virulence 2. Repels antimicrobial peptides within NETs	Kristian et al., 2003)
		Helicobacter pylori	Addition of ethanolamine residue to the C1 hydroxyl to dephosphorylate lipid A	1. Increase resistance to antimicrobial peptides; 2. Promotes persistence in the gastric mucosa	Tran et al., 2006
		H. influenzae	The addition of phosphorylcholine to LPS permits survival to LL-37 as promotes repulsion charges	Resistance to antimicrobial peptides	Lysenko et al., 2000
	Neutrophil activation inhibition	*Acinetobacter baumannii*	Decreases neutrophil recognition by suppressing CD11a expression	1. Decreases the chemotactic capacity of the neutrophil; 2. Escapes the host defenses and cause infections; 3. Inhibits NETs formation	Kamoshida et al., 2018
	Collagen-like protein-1	*Streptococcus pyogenes* serotype M1T1	Suppresses Myeloperoxidase release by neutrophils	1. Limits the formation of NETs; 2. Provides resistance to LL-37 within the NETs	Döhrmann et al., 2014
	Adenylate cyclase toxin	*Bordetella pertussis*	a) Inhibits respiratory burst in neutrophils; b) Prevents granule migration toward neutrophils nucleus	Inhibits NETs formation	Eby et al., 2014
	Streptolysin O	Group A *Streptococcus*	a) Inhibits respiratory burst in neutrophils; b) Prevents release of neutrophil elastase and IL-8; c) Induce apoptotic cell death of neutrophils	1. Affects NETs formation; 2. Increases virulence in the bloodstream	Uchiyama et al., 2015
Suppression/ Inhibition	Eap	*S. aureus*	a) Blocks activity of neutrophil serine proteases (e.g. Neutrophil Elastase); b) Exhibits DNA-binding activity	1. Favors the adhesion of bacteria to the host tissue, in the context of inflammation and wounds; 2. Modulates the formation and stability of NETs	Eisenbeis et al., 2018
	SAK (Staphylokinase)	*S. aureus*	a) Staphylokinase directly interacts with the host innate immune system, facilitate bacteria to bind host plasminogen through bacterial cell surface receptors; b) Neutralizes activity α-defensins, effector molecules of the innate immune system and antimicrobial proteins within NETs	1. Promote invasion of host tissues; 2. Increases protection against NETs components	Jin et al., 2004
	Elastase	*P. aeruginosa*	Degrades LL-37	1. Prevents bacterial killing	Schmidtchen et al., 2002
	Metalloproteinase	*Proteus mirabilis*	Degrades lactoferrin within NETs	Increases protection against NETs components	Schmidtchen et al., 2002
	Catalase	*H. influenzae*	a) Inhibits respiratory burst in neutrophils	Inhibits NETs formation	Juneau et al., 2015a
	RodA	*Aspergillus fumigatus*	Promotes masking of immunologically active components of fungi	Reduction of NETs formation	Bruns et al., 2010

among the most abundant polysaccharides in *C. albicans* (Pierce et al., 2017). Pathogens' size is a characteristic that neutrophils detect to initiate the formation of extracellular traps (Branzk et al., 2014); and due to this NETs formation is considered as a strategy by which neutrophils respond to biofilms (Rybtke et al., 2015). Biofilms can be modified to evade recognition and removal by neutrophils (Table 1). In this regard, a decrease in NETs formation was observed when neutrophils were incubated with *C. albicans* biofilms, possibly due to the masking of epitopes in the yeast cell wall. Epitopes are recognized by neutrophils to generate extracellular traps due to the matrix of polysaccharides present in the biofilm or through the activation of alternative pathways in the neutrophil that could generate a decreased induction of NETs (Johnson et al., 2016). Additional studies have shown that *S. suis* serotype 2 can prevent phagocytosis and NETs formation through biofilm formation, unlike its planktonic state, where NETs can effectively eliminate this pathogen (Ma et al., 2017).

Another aspect that may be relevant in the recognition of pathogen biofilms by neutrophils is the stage of maturation of these structures. Unlike immature biofilms, mature biofilms can have complex architectural characteristics, including three-dimensional microcolonies surrounded by the matrix of polysaccharides and liquid channels. Additionally, it is also known that during biofilm maturation, the microbial community develops a higher synthesis of polymeric substances, resistance to antibiotics, higher resistance to ultraviolet light, increased genetic exchange, and higher production of secondary metabolites, hindering its recognition by immune cells (O'Toole et al. 2000). This is supported by reports in which mature fungal biofilms with β-glucans in the matrix of extracellular polymeric substances, do not promote reactive oxygen species formation (ROS) by neutrophils (Xie et al., 2012), which are also important mediators for the induction of some forms of NETs, similar to mature staphylococcal biofilms. In line with this, the survival of non-typable *Haemophilus influenzae* in the presence of NETs depends on the expression of sialylated lipooligosaccharide glycoforms, present in mature biofilms (Hong et al., 2009).

Of particular relevance, is that some pathogens can even take advantage of NETs for their benefit, since *in vitro* studies have shown that *P. aeruginosa* biofilms promote the release of NETs, and then incorporate the released DNA into their polysaccharide matrix, generating tolerance to antimicrobial peptides embedded in the DNA lattice (Rybtke et al., 2015). In an *in vivo* model, *S. pneumoniae* biofilms contain neutrophil DNA fibers functioning as scaffolds for the establishment of bacteria (Reid et al., 2009). In addition, the strains of methicillin-resistant *S. aureus* after biofilm formation secrete pore-forming enzymes (e.g.leukocidin), which induce the release of NETs with low bactericidal activity, preventing elimination by other neutrophil-mediated mechanisms (Bhattacharya et al., 2018).

5.3. Cell surface modification

Neutrophil antimicrobial peptides such as defensins and cathelicidins (LL-37), exhibit electrostatic affinity, binding to negatively charged phospholipids (phosphatidylglycerol, cardiolipin, and phosphatidylserine) of pathogen membranes, thereby promoting death (Cole and Nizet, 2016). However, some pathogens modify their cell surface by incorporating positively charged residues to decrease the affinity to antimicrobial proteins, thus evading their activity (Table 1) (Kristian et al., 2005).

Some Gram-positive pathogens, such as *S. aureus*, can modify teichoic acids by incorporating an amino acid D-alanine through the activation of the dlt operon, resulting in a significant reduction of the negative charge in the cell wall. This change increases its resistance to the activity of antimicrobial proteins or neutrophil lysozyme and has also been shown to promote the death of polymorphonuclear cells (Peschel et al., 1999). Such a modification is also observed in Group A *Streptococcus* and *Listeria monocytogenes*, which incorporate D-alanine to the lipoteichoic acid of the membrane (Kristian et al., 2005). Likewise, Gram-negative pathogens such as *Salmonella enterica* can modify the lipid A of the lipopolysaccharide by adding 4-aminoarabinose molecules through the activation of the two-component system PhoP-PhoQ, promoting a cell wall with a diminished positive charge that results in a lower binding to antimicrobial peptides and bactericidal/permeability enhancer protein (BPI), in addition to acquiring to antibiotics resistance whose target is the bacterial cell wall (Gunn et al., 2000).

Resistance to antimicrobial peptides also occurs in *S. aureus*, therefore increasing invasiveness and virulence (Kristian et al., 2003). This activity is mediated by the MprF membrane protein that allows the synthesis of lysylphosphatidylglycerol, a phosphatidylglycerol to which positively charged L-lysine is added. This modification results in increased resistance to the activity of defensins. *Helicobacter pylori* employ a strategy based on the dephosphorylation of lipid A of LPS with the addition of phosphoethanolamine, contributing to the reduction of negative charge and resistance to neutrophil cationic peptides, as well as antibiotics such as polymyxins (Tran et al., 2006). Likewise, the addition of phosphorylcholine in *H. influenzae* in the oligosaccharide region confers resistance to the effect of cathelicidin (LL-37 / hCAP18) increases its survival (Lysenko et al., 2000).

5.4. Suppression/Inhibition of NETs formation

The expression and secretion of virulence factors by microorganisms allows them to colonize and invade tissues, to obtain nutrients, as well as to escape the innate immune response mediated by neutrophils and other cells of the immune system. Various functions have been described for proteins secreted by pathogens, such as a high capacity to cleave and inactivate antimicrobial peptides, factors that can attenuate the respiratory burst in neutrophils, thus reducing netosis; nucleases that allow them to escape from the capture and elimination mediated by NETs; and proteins promoting the activation of inhibitory leukocyte receptors (Fig. 1 and Table 1) (Joo et al., 2016; Storisteanu et al., 2017; Teng et al., 2017).

Recently, some other functions have been elucidated for various proteins secreted by pathogens. It has been shown that membrane proteins (e.g., LPS) or polysaccharides that are secreted to the extracellular medium directly bind and neutralize some antimicrobial proteins present in neutrophils (Cole and Nizet, 2016). In other pathogens (e.g. *H. influenzae*) interacting with neutrophils, catalases are secreted to degrade hydrogen peroxide produced during phagocytosis or the formation of extracellular traps; other enzymes such as superoxide dismutase and glutathione peroxidases that possess the ability to neutralize the oxidative response of neutrophils, are also secreted (Urban et al., 2006).

It has been recently described that some pathogens have developed strategies aimed at inhibiting NETs. The expression of toxin adenylate cyclase (ACT) for the production of pertussis toxin by *Bordetella pertussis*, generates an increase of intracellular cyclic adenosine monophosphate (cAMP), resulting in inhibition of the respiratory burst involved in the NETs formation (Eby et al., 2014; Burgener and Schroder, 2019). Similarly, streptolysin O (SLO) produced by *S. pneumoniae* can suppress various functions in neutrophils, such as respiratory bursts, migration, degranulation, and extracellular trap formation (Uchiyama et al. 2015). It is known that the scl-1 gene in *S. pyogenes* encodes for a surface protein that has a collagen-like domain named Collagen-Like Protein 1). This protein participates in the formation of biofilms, and in binding to host proteins involved in pathogenesis. Its expression, however, also alters the neutrophil-mediated immune response by inhibiting phagocytosis, limiting the formation of NETs, and suppressing the activity of myeloperoxidase (MPO) contained in extracellular traps (Döhrmann et al., 2014). Similarly, in *S. aureus*, staphylokinase protein (SAK) and extracellular adhesion protein (Eap) are important in the resistance against neutrophils; SAK neutralizes the effect of α-defensins (human neutrophil peptides 1 and 2) (Jin et al., 2004), while Eap mediates resistance against NETs, protecting *S. aureus* from capture in these structures by binding to the DNA scaffold, modifying its stability and also blocking the activity of the granular NETs neutrophil elastase contained (Eisenbeis et al., 2018).

Other pathogens capable of suppressing the bactericidal effect of NETs are *P. aeruginosa* and *Proteus mirabilis*, which through the activity of bacterial elastase and a metalloproteinase of 50 kDa, respectively, promote the hydrolysis of cathelicidin and lactoferrin granules (Schmidtchen et al., 2002). Some other pathogens inhibit their recognition by neutrophils by promoting alterations in membrane receptors present in these cells. In this regard, *Acinetobacter baumannii* promotes suppression of CD11 expression in neutrophils, leading to a state of low activation that is reflected in decreased NET formation (Kamoshida et al., 2018). Fungal microorganisms, such as *Aspergillus fumigatus*, have developed strategies to avoid their elimination by neutrophils. Thus, RodA expressed protects conidia from recognition by cells of the immune system, also promoting reduction in the formation of NETs, although the mechanism by which it achieves such a decrease is still unknown, it has been proposed that RodA could cover some antigenic components of the fungal cell wall, diminishing their recognition by neutrophils (Bruns et al., 2010).

6. Concluding remarks

Neutrophils are the first cells of the immune system that reach the site of infection and promote the elimination of pathogenic microorganisms through various mechanisms, including the formation of extracellular traps (NETs). Initially, phagocytosis and degranulation were considered to be the main mechanisms carried out by neutrophils to eliminate pathogens, however, the description of pathogen molecules with the capacity to inhibit, degrade and evade the antimicrobial activity of NETs highlights the importance of these structures in the immune response. Since the result of the interaction between neutrophils and pathogens can be decisive in the establishment or resolution of infectious processes, the characterization of the mechanisms that

pathogens use to evade their containment and elimination by NETs is of utmost importance for the establishment of more effective treatments

Funding

This research was supported by grant A1-S-9424 from SEP-CONACYT Basic Scientific Research 2017-2018 Fund for Education.

CRediT authorship contribution statement

A.L. Ríos-López: Writing - original draft. **G.M. González:** Writing - review & editing. **R. Hernández-Bello:** Writing - review & editing. **A. Sánchez-González:** Conceptualization, Writing - review & editing.

Declaration of Competing Interest

The authors declare no conflict of interest

Acknowledgments

We thank the members of the Microbiology Department at the School of Medicine of the Universidad Autónoma de Nuevo León in México for their support and advice during the preparation of this review. We also thank Luis Antonio Sánchez González, Ph.D. from the School of Sciences of the Universidad Nacional Autónoma de México (UNAM) and Dr. Sergio Lozano of the "Dr. José E. González" University Hospital (Monterrey, México) for their help in reviewing the manuscript.

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