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# Pathogenesis of *Neisseria gonorrhoeae* in the female reproductive tract: Neutrophilic host response, sustained infection, and clinical sequelae

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## Abstract

**Purpose of Review—**Gonorrhea is a major global health concern, caused by the bacterium *Neisseria gonorrhoeae*. The main clinical feature of acute gonorrhea is neutrophilic influx that is unable to clear infection. Women of reproductive age are predominantly at risk for serious sequelae of gonorrhea, including pelvic inflammatory disease, ectopic pregnancy, and infertility. This review will highlight how neutrophils are recruited to the female reproductive tract (FRT) in response to *N. gonorrhoeae*, how *N. gonorrhoeae* resists killing by neutrophils, and the connection between neutrophilic inflammation and cellular damage.

**Recent Findings—**Epithelial cells and immune cells of the FRT recognize and respond to *N. gonorrhoeae* lipid A and heptose bisphosphate of lipooligosaccharide, porin, lipoproteins, and peptidoglycan fragments. *N. gonorrhoeae* skews the resulting immune response towards an neutrophilic, Th17-like response. *N. gonorrhoeae* has multiple, non-redundant mechanisms to survive inside neutrophils and in neutrophil extracellular traps. Infection that ascends to the upper FRT induces the further release of inflammatory cytokines and matrix metalloproteinases, which cause epithelial damage.

**Summary—***N. gonorrhoeae* is remarkable in its ability to recruit neutrophils, yet survive in their midst. New models being developed for FRT infection with *N. gonorrhoeae* will be useful to reveal the mechanisms underlying these observations.

### Keywords

neutrophil; *Neisseria gonorrhoeae*; female reproductive tract; inflammation; infectious diseases

## INTRODUCTION

The Gram-negative diplococcus *Neisseria gonorrhoeae* (the gonococcus or Gc) causes the sexually transmitted infection gonorrhea, with an estimated 78 million cases worldwide each year [1]. Increasing rates of infection, the emergence of multidrug-resistant strains, and the lack of a protective vaccine have prompted the CDC and WHO to classify Gc as a top infectious threat [1]. Women are particularly at risk for negative outcomes associated with

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gonorrhea, including pelvic inflammatory disease (PID), ectopic pregnancy, and infertility [2].

Infection elicits a robust inflammatory response featuring the influx of neutrophils. Despite this potent immune response, secretions from infected individuals contain viable bacteria, many of which are associated with neutrophils [3]. Sustained neutrophil influx in other infectious conditions has been linked to epithelial cell damage and pathology associated with disease [4,5,6]. We posit that the ability of Gc to elicit neutrophilic inflammation in the female reproductive tract (FRT) is central to its ability to persist within its obligate human host and be transmitted to new hosts, while contributing to the negative outcomes in women. **This review will highlight recent contributions to our understanding of the neutrophilic inflammatory response to Gc in the FRT, the infection models underlying these discoveries, and opportunities for the field moving forward.**

## GC STIMULATES A NON-PROTECTIVE NEUTROPHILIC INFLAMMATORY RESPONSE IN THE FRT

The initial site of Gc infection in women is the endocervix, the transition from the lower to upper FRT (Figure 1). Despite neutrophilic cervicitis, the majority of women with cervical gonorrhea do not report symptoms [reviewed in 7,15]. Although genital mucosal secretions contain cationic antimicrobial peptides (CAMPs) and other bactericidal components, Gc survives in their midst (Figure 1). The MisR-MisS two-component regulatory system confers inducible resistance in Gc to CAMPs by directing the expression of genes important for envelope integrity [12*], which enhances Gc colonization and extends infection duration in a mouse model of lower FRT gonorrhea [13*].

The recruitment and activation of neutrophils in response to Gc is coordinated by cellular and soluble factors. In the FRT, Gc interacts with epithelial and immune cells, including macrophages, dendritic cells, T cells, and neutrophils, to elicit the local production of inflammatory mediators and activation of a Th17-type response (Figure 2) [27,28,29,30*]. Moreover, Gc infection was recently shown to activate non-muscle myosin II in human cervical tissue, leading to epithelial junctional disruption, exfoliation of endocervical cells, and bacterial subepithelial penetration [31*].

### PRR activation by Gc PAMPs

During infection, cytokine production is driven by signaling via epithelial and resident immune cell pattern recognition receptors (PRRs) that recognize Gc pathogen-associated molecular patterns (PAMPs) (Figure 2). Levels of PRRs, particularly TLR4, which recognizes the lipid A moiety of Gc lipooligosaccharide (LOS), and numbers of myeloid cells both increase from the lower to upper FRT, such that an immune response is mounted only to pathogens that ascend into the upper FRT and not to the resident microbiota of the lower FRT (Figure 1). PRRs include membrane-associated Toll-like receptors (TLRs) and cytoplasmic NOD-like receptors (NLRs) that recognize a variety of Gc PAMPs (Figures 1 & 2) [22,32,33]. Recent work from Gray-Owen and colleagues has identified a new PAMP from Gc, the LOS biosynthesis pathway intermediate heptose-1,7-bisphosphate (HBP)

[24**,25,26*]. Activation of NFkB signaling by HBP occurs via phosphorylation-dependent oligomerization of TRAF-interacting protein with forkhead-associated domain (TIFA) [24**]. Recognition of HBP represents a novel mechanism to detect and mount an immune response to Gram-negative bacterial pathogens [26*]**;** this may be particularly important for signaling in sentinel cells that lack TLR4 expression, such as cervical epithelial cells.

## Gc modulates innate immune cell responses

There is strong evidence to suggest that Gc skews innate immune cell recognition and response as an element of its survival strategy. Addition of phosphoethanolamine (PEA) to lipid A by the enzyme LptA, which is found in the pathogenic *Neisseria*, not only enhances TLR4 recognition to stimulate NFkB-driven cytokine production, but also aids the bacteria in defense against CAMPs found in mucosal secretions and neutrophils [10,34,35*]. Therefore, the potentially damaging effects of lipid A-mediated activation of TLR4 and subsequent inflammation are mitigated by the intrinsic defense against killing that is conferred by modifying lipid A with PEA. Another example was recently elucidated by Golenbock and colleagues, who showed that exposure to Gc leads to STING-dependent activation of the intracellular DNA sensor cyclic GMP-AMP synthase (cGAS) in monocytes and macrophages [36**]. In combination with TLR4 activation, this stimulates the production of IFN-β. Rather than helping to control infection, IFN-β increases the availability of intracellular iron in macrophages and neutrophils, which is correlated with enhanced survival of Gc [36**]. Gc may have additional mechanisms to survive and replicate in association with macrophages [37*], including through the expression of surface-exposed factors such as macrophage infectivity potentiator-like protein (MIP) [38,39*].

Not all features of Gc are immunostimulatory. Gc has been reported to polarize macrophages to an immune-regulatory, M2 phenotype, which would downregulate the antimicrobial activity and proinflammatory cytokine production of macrophages [40*]. Moreover, while the peptidoglycan (PG) fragments released by Gc are toxic to Fallopian tube cells, they are poorly recognized by innate immune receptors. Specifically, Duncan and Dillard and colleagues recently found that the PG monomers released by Gc, via the activities of the lytic transglycosylases LtgA and LtgD, are poor activators of mouse NOD2 and TLR2, compared with multimeric PG. This is due to the anhydro moiety on the terminus of Ltg-cleaved fragments, rather than a free reducing (hydroxyl) end, as would be found following digestion by lysozyme [41**]. These studies suggest that the large amounts of PG fragments released by Gc during normal growth may serve as decoys, to limit PRR activation in the lower FRT and enhance overall Gc survival.

## Gc manipulates the adaptive immune response, skewing the inflammatory environment to attract and activate neutrophils

Despite the proinflammatory nature of Gc PAMPs, the subsequent host immune response is not sufficient to clear infection. Gc has a remarkable ability to evade host antibody-mediated immunity, due to extensive antigenic and phase variation of its immunogenic surface structures as well as by expression of Rmp, which limits the generation of bactericidal antibodies [42,43]. Gc also manipulates cellular immune responses to limit adaptive immune

cell activation and direct the immune response towards a neutrophilic, non-protective presentation, as described below.

**CEACAM1-mediated limitation of immune cell activation—**Most members of the family of opacity-associated (Opa) outer-membrane proteins of Gc interact with human CEACAM1, which is expressed on T cells, B cells, dendritic cells, and epithelial cells. CEACAM1 has an immunoreceptor tyrosine-based inhibition motif on its cytoplasmic tail, which recruits the SHP phosphatase to block signaling *in trans* from activating receptors [44]. Engagement of CEACAM1 by Opa+ Gc also drives bacterial internalization into epithelial cells, within which Gc can survive while avoiding exposure to CAMPs, antibodies, complement factors, and other bactericidal components. The importance of the Opa-CEACAM1 interaction to the pathogenesis of gonorrhea is reflected in the strong selection for CEACAM1-binding Gc *in vivo* [45**]. However, the *opa* genes phase-vary at high frequency and diversify by recombination and mutation, changing their ability to engage CEACAM1 [46].

**TH17 response—**Gc infection induces the local production of TGF-β and IL-10 to skew the resulting adaptive response away from Th1 and Th2-driven immunity and towards a Th17 response, which in the context of gonorrhea enhances inflammation and prevents the development of protective immunity [47,48,49,15]. Th17 cells produce IL-17, which is important for neutrophil recruitment in the human and mouse lower FRT in response to Gc [30*,50]. The Russell group has proposed reorientation of the T cell response to Gc away from Th17 and towards Th1 as a therapeutic intervention to ameliorate neutrophilic inflammation. In support of this possibility, female mice immunized with Gc antigens in combination with IL-12, a Th1-activating cytokine, clear Gc more rapidly when first infected and are protected against reinfection [51**].

## GC THWARTS NEUTROPHIL FUNCTIONS TO ENHANCE ITS SURVIVAL AND PROMOTE CONTINUED INFLAMMATION

The predominant clinical feature of acute gonorrhea is the presence of viable Gc in association with neutrophils in mucosal secretions. While neutrophils have a robust antimicrobial arsenal (Figure 3), our laboratory and others have identified mechanisms Gc uses to evade killing by neutrophils (Figure 3 & Table 1). Antimicrobial components are a crucial part of neutrophils' functionality, but they have the potential to damage host cells. Reactive oxygen species (ROS) oxidize lipids, proteins, and DNA, and also serves as a second messenger to enhance inflammation and neutrophil recruitment [71]. Proteases, including neutrophil-derived matrix metalloproteases, degrade tissue extracellular matrix and contribute to sustained neutrophil recruitment [reviewed in 5]. The CAMP LL-37 interacts with host cell receptors including TLR4 and contributes to their continued activation during infection and inflammation [72]. Histones, released from neutrophils in neutrophil extracellular traps (NETs), induce direct epithelial cell damage [73]. NETs are also thought to contribute to the pathology associated with autoimmune diseases by providing self-antigen (such as in Systemic Lupus Erythematosus), and with cardiovascular disease by enhancing formation of atherosclerotic plaques [74,75]. NETs are formed in

response to Gc, but the bacteria have multiple mechanisms to survive in association with NETs, including expression of a nuclease (Nuc) that degrades NET DNA (Figure 3 & Table 1) [59*,60*,61*]. Although the contribution of Gc-induced NETs to cellular damage remains to be elucidated, it is likely that Nuc could release CAMPs and histones from NETs, to directly damage epithelial cells and stimulate continued inflammation.

## Gc defenses against neutrophils also modulate neutrophil activation

Some of the defenses used by Gc against neutrophil antimicrobial activities influence neutrophil activation and extracellular release of antimicrobial components (Figure 3). These components may contribute to the cellular damage associated with gonorrhea in the FRT.

Variations in Opa protein expression contribute to neutrophil activation and the ability of Gc to survive exposure to neutrophils. A subset of Gc express Opa proteins that interact with CEACAM3, which unlike CEACAM1 has an immunoreceptor tyrosine-based activation motif (ITAM) in its cytoplasmic tail. Interaction with CEACAM3 on neutrophils leads to increased ROS production and granule release, and decreased Gc survival (Figure 3) [52,53,54,55*,56]. Engagement of CEACAM3 also serves to further recruit and activate neutrophils at the site of infection *in vivo* [55*,56]. The same study that found a selection for an Opa protein repertoire that binds CEACAM1 also found a selection against CEACAM3-binding Opa proteins, underscoring the importance for Gc of avoiding recognition by this receptor [45**].

Some Gc defenses also limit the degree of granule fusion with phagosomes and the plasma membrane. We recently reported that addition of PEA to LOS by LptA is important for survival of Gc from neutrophils, not only by defending against CAMPs, but also by limiting the extent of phagolysosome formation [35*]. This was surprising since PEA-modified lipid A has a higher affinity for TLR4 [34], suggesting the activation of neutrophils by Gc may be TLR4-independent. As another example, we found the PG modifying enzymes LtgA and LtgD defend Gc from neutrophils, particularly from killing by lysozyme, and limit granule fusion with phagosomes and the plasma membrane [62**]. This observation is in agreement with recent findings that PG fragments produced by LtgA and LtgD are nonstimulatory for NLRs and TLRs [41**].

## Challenges in modeling ascending infection with Gc and the consequences of neutrophil influx

A direct role for neutrophils in inducing epithelial cell damage in gonorrhea has not yet been described, owing to challenges of studying Gc infection and neutrophilic inflammation in the FRT. Ex vivo systems such as cell lines and tissue explants do not generally incorporate neutrophils, although basal-to-apical transepithelial migration in response to other mucosal pathogens has been modeled with monolayers of polarized epithelial cells [76]. A mouse model of lower FRT infection has been established by the Jerse group and used to probe the bacterial and host factors that are important for colonization and early neutrophil recruitment [77]. Subsequently, Gc infection models using mice transgenic for human receptors and other human-specific components have been developed. In particular, in mice that are transgenic for human CEACAMs, the Gray-Owen group has reported that Gc robustly

infects the lower FRT and triggers a strong influx of CEACAM-expressing neutrophils that interact with the bacteria [56]. While mouse models have increased our understanding of Gc colonization and early inflammatory responses, at this time they do not reproduce features of Gc infection seen in women, including ascending infection, sustained neutrophil influx, and epithelial damage.

## NEUTROPHILIC INFLAMMATION AND EPITHELIAL DAMAGE IN RESPONSE TO GC IN THE UPPER FRT

If treatment of Gc infection does not occur or is ineffective, Gc can ascend to the upper FRT, where the neutrophilic inflammatory response is more potent; this is correlated with increased epithelial expression of pattern recognition receptors (PRRs) and greater numbers of resident myeloid cells that are poised to detect foreign antigens (Figure 1) [14]. The interactions of Gc with epithelial cells during ascent from the lower to the upper FRT have recently been simulated using human Hec-1-A cells cultured in a bioreactor as three-dimensional organoids [78**]. Gc infection, but not colonization with commensal *Lactobacillus crispatus* or *Gardnerella vaginalis*, stimulates production of proinflammatory mediators (IL-1β, IL-8, and TNF-α) and alterations to host cells, including microvillus remodeling [78**].

A hallmark of upper FRT infection with Gc is the death of ciliated cells lining the Fallopian tube. Reduced motility in the Fallopian tube, along with tubal scarring, result in infertility and ectopic pregnancy. Human Fallopian tube explants have been instrumental in demonstrating that release of LOS and PG fragments by Gc stimulate the production of inflammatory cytokines and second messengers, including TNF-α and nitric oxide [79,80,81]. Unlike most bacteria, including other *Neisseria* species, Gc poorly recycles its PG during cell wall turnover [82]. Instead, PG fragments are released extracellularly and are responsible for ciliated cell death [83**,22]. A new contributor to Fallopian tube damage was recently reported by Velazquez, Christodoulides and colleagues [84**]. Gc-infected Fallopian tube epithelial cells increase production of matrix metalloproteinases (MMPs) and extracellular release of MMP-9 [84**], which may amplify tissue destruction by degrading extracellular matrix and interfering with tissue repair. Further, MMP-9 generates chemokine mimetics and extracellular matrix fragments, which further stimulate inflammation and neutrophil recruitment. Neutrophils themselves are a significant source of MMP-9, setting up a vicious cycle of inflammation and epithelial cell damage [5].

Much remains to be learned about the mechanisms underlying Gc-induced neutrophilic inflammation and damage in the upper FRT. It is unethical to conduct human challenge studies on women due to the risk of serious complications. Fallopian tube explants and endometrial organoids are useful models, especially if primary human neutrophils are introduced. A new female mouse model of upper FRT infection with Gc provides an *in vivo* platform for studying neutrophilic inflammation and its consequences [85**]. In this model, transcervical inoculation of Gc leads to infection of the uterine horns and corpus of the upper FRT, resulting in robust and rapid neutrophilic infiltration, edema, and other signs of PID [85**]. The inflammatory process is exaggerated in mice in diestrus; similarly, PID

most commonly presents after the onset of menses in women with gonorrhea [85**]. Introduction of transgenic or knockout mice into this model may enable longer-term infection with Gc, to model the chronic inflammation and consequent damage associated with PID.

## CONCLUSION

Gc induces potent neutrophilic inflammatory responses, yet survives in their midst. Sustained infection and neutrophilic inflammation likely underlie the pathology associated with gonorrhea in women. Recently developed models of infection provide new platforms for studying neutrophil influx, measuring consequent epithelial cell damage, and testing novel therapeutics to thwart the non-productive, sustained neutrophil response to Gc. Genetic manipulation of mouse and human cells will facilitate mechanistic studies of the pathways driving neutrophil influx and host damage. These advances will enable a better understanding of how sustained neutrophilic inflammation in response to Gc drives epithelial damage and serious clinical sequelae in women.

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**KEY POINTS**

- *N. gonorrhoeae* infection stimulates a robust inflammatory response featuring the recruitment and activation of neutrophils.
- *N. gonorrhoeae* has mechanisms to resist and thwart neutrophil antimicrobial activities, while promoting neutrophil production and release of proinflammatory products.
- Sustained neutrophil influx in response to *N. gonorrhoeae* is linked to host epithelial damage and serious sequelae in women with gonorrhea.

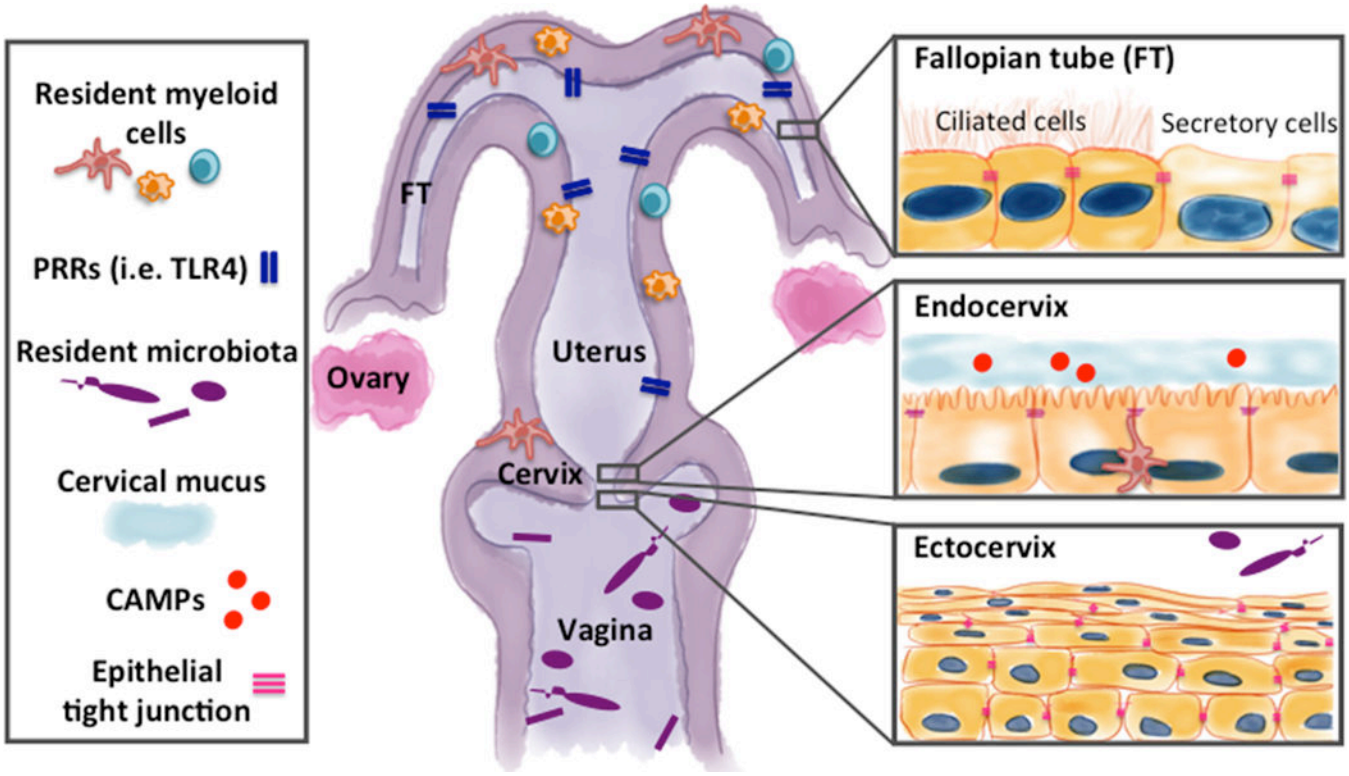


**Figure 1. Gc initially infects the endocervix, a transition from the lower FRT to the upper FRT**

The endocervix marks a transition from multilayered squamous epithelium lining the lower FRT to single columnar epithelium lining the upper reproductive tract. Epithelial cells provide a number of barriers to infection including maintaining epithelial tight junctions and barrier integrity, producing thick cervical mucus, and producing and secreting cationic antimicrobial peptides (CAMPs) that accumulate in cervical mucus [reviewed in 8]. Gc factors contributing to survival from CAMPs in the genital tract include expression of the MtrCDE efflux pump, modification of lipid A with phosphoethanolamine (see Table 1 for more information) [9,10,11], and the MisR-MisS two-component regulatory system [12*, 13*]. The transition from the lower to the upper FRT is also marked by changes in microbiota, pattern-recognition receptor (PRR) expression, and myeloid cell frequency [reviewed by 14]. While the lower FRT has a resident microbiota, low PRR expression, and low myeloid cell frequency, the upper FRT is considered sterile and has increased PRR expression and myeloid cell frequencies.

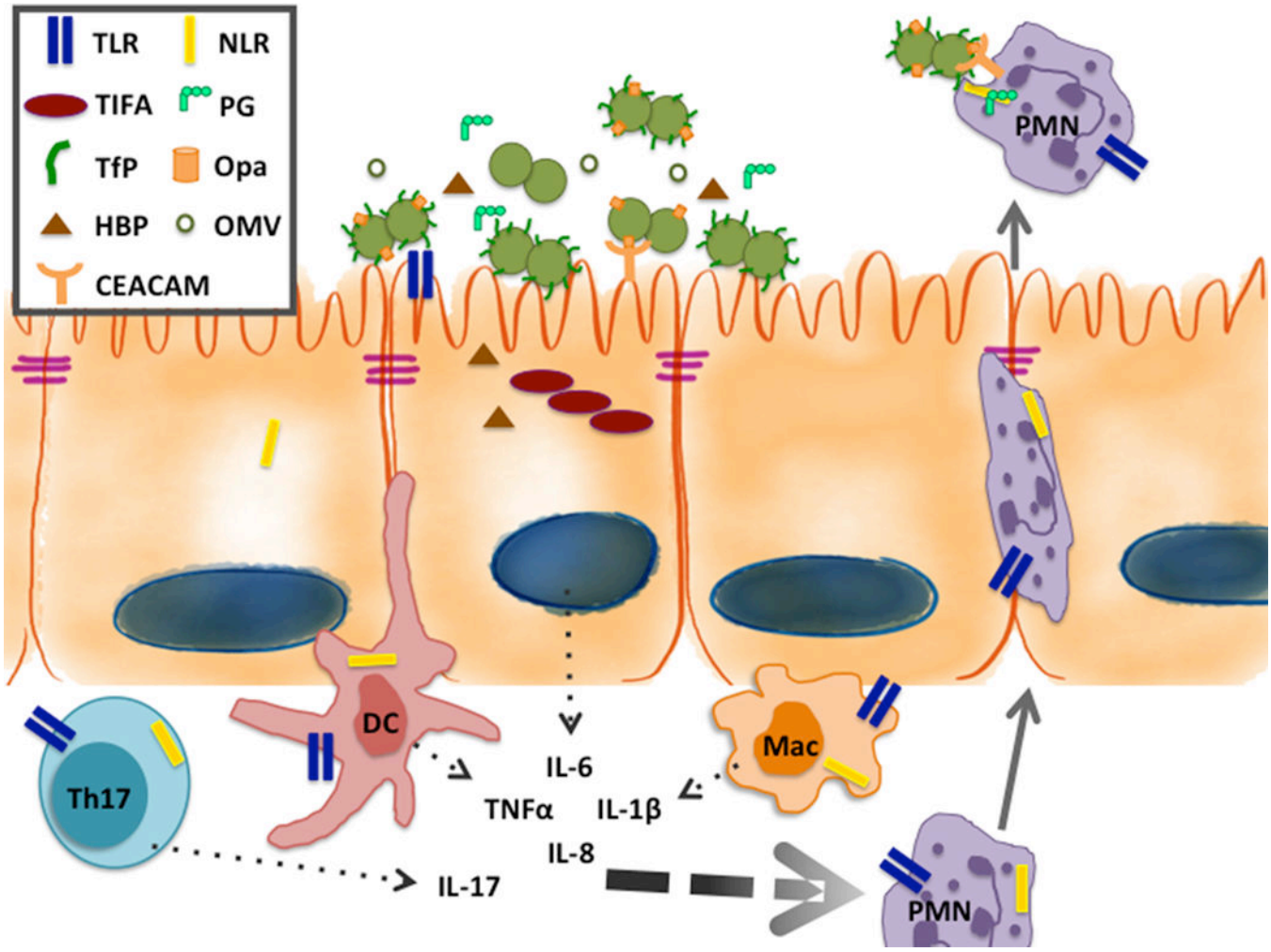


**Figure 2. Epithelial and resident immune cells initiate the immune response to Gc**

Gc uses adhesins such as type IV pili and opacity-associated (Opa) proteins to interact with the epithelial cells lining the human FRT [reviewed in 7]. The roles of several important Gc surface structures, including opacity associated (Opa) proteins, the type IV pilus (TfP), lipooligosaccharide (LOS), and porin, have been well defined in mediating adherence, invasion, and host cell signaling. During infection, there is a mixture of Gc with varied expression of Opa proteins and the TfP. Opa proteins interact with CEACAMs on host epithelial and immune cells to influence adherence, internalization, and signaling. PRRs on epithelial and resident immune cells recognize PAMPs presented on the surface of Gc and/or released from the bacterium freely or as components of outer membrane vesicles (OMVs). In addition to well-known PAMPs such as lipooligosaccharide (LOS) and PG, the Gc cell envelope and outer membrane vesicles (OMVs) may harbor additional factors that affect the host response to infection [16]. Cervical epithelial cells respond to Gc through stimulation of TLR2 but not TLR4, while resident immune and upper FRT cells, including fallopian tube epithelial cells, are particularly poised to respond to LOS via TLR4 [17,18]. Gc porin and other lipoproteins stimulate TLR2 to activate NFkB-driven inflammatory cytokine production [19,20]. Similarly, TLR4 is potently activated by the lipid A portion of LOS from

Gc and its close relative, *Neisseria meningitidis* [reviewed in 21]. While surface-expressed TLRs recognize Gc LOS, porin, and other lipoproteins, PG is primarily recognized by intracellular receptors. The best-described intracellular receptors for PG are NOD1, which recognizes gamma-glutamyl-diaminopimelic acid, and NOD2, which recognizes muramyl dipeptide [reviewed in 22]. These receptors are expressed in epithelial cells as well as sentinel innate immune cells. Human NOD1 and NOD2, and mouse NOD2, recognize and mount an NF-kB-driven innate immune response to PG from Gc, in the context of whole bacteria or to PG fragments in conditioned media [23]. An additional mechanism of intracellular detection of gram-negative bacteria is the TIFA-dependent detection of heptose-1,7-bisphosphate (HBP), an intermediate in LPS/LOS production [24**,25,26*]. As a result, epithelial and resident myeloid cells secrete pro-inflammatory cytokines, including TNFα, IL-1β, IL-6, and IL-8 and sentinel Th17 cells release IL-17. The combination of these cytokines creates a cytokine gradient that serves to recruit neutrophils from the bloodstream and activate them at the site of infection.

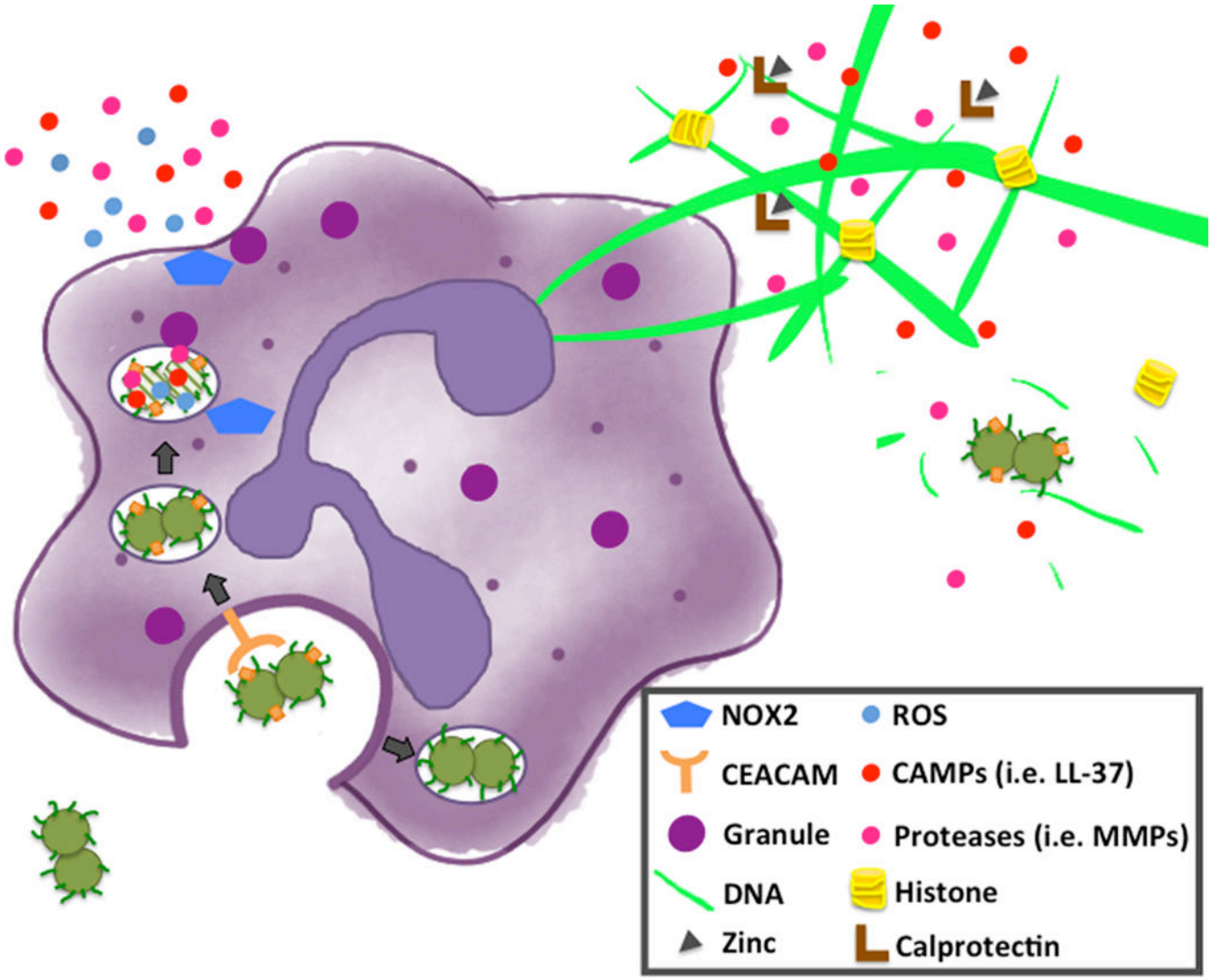


**Figure 3. Neutrophils possess an arsenal of extracellular and intracellular killing mechanisms that Gc can evade, leading to off-target host cell damage**

Neutrophil killing mechanisms include phagocytosis, production of reactive oxygen species (ROS), degranulation, and neutrophil extracellular trap (NET) formation. Granule components include cationic antimicrobial proteins (CAMPs; i.e. LL-37) and proteases (i.e. MMPs). Gc has evolved elegant mechanisms to resist neutrophil killing [see 3, 27 for overviews]. An important example is variation in Opa protein expression, which can affect neutrophil activation and Gc survival. In women, Gc expressing Opa proteins are predominantly recovered during the follicular phase of the menstrual cycle, while Opa-negative Gc predominate in the luteal phase and in upper FRT infection [7]. Opa-expressing Gc are phagocytosed in a CEACAM-dependent manner and trafficked to mature phagosomes while Opa-deficient Gc survive longer in immature phagosomes. Opa+ Gc that interact with CEACAM3 stimulate opsonin-independent phagocytosis, Syk and PI3 kinase dependent degranulation, ROS production, and fusion of granules to the phagosome, resulting in bacterial intracellular killing [52,53,54,55*,56]. In contrast, Opa-negative Gc is

also internalized by adherent human neutrophils in an opsonin-independent manner, but suppresses ROS production and limits phagosome-granule fusion [57,58,54]. Our lab and others have recently uncovered additional mechanisms of resisting neutrophil killing including resistance to antimicrobial compounds contained in granules released at the plasma and phagosomal membranes and as components of NETs formed in response to Gc [35,59*,60*,61*,62*]. We and others have found that Gc stimulates NET formation [59*, 61*]. However Gc encodes a thermonuclease (Nuc) that is released extracellularly and is necessary and sufficient for Gc to degrade the DNA backbone of NETs [59*]. Additionally, Gc uses the TonB-dependent transporter TdfH to obtain Zn from calprotectin, a protein that is abundant in the neutrophil cytosol and NETs [60*]. Gc stimulation of NET formation does not require an oxidative burst or ROS [61*]. Nuc and TdfH, along with the LOS-modifying enzyme LptA, enhance Gc survival in association with NETs [59*,60*,35*]. Further resistance to graunule components is conferred by phosphoethanolamine (PEA) addition to the lipid A moiety of LOS by LptA [35*] and envelope integrity maintained via PG modification by LtgA and LtgD [62**]. Since Gc can evade neutrophil killing, reactive products generated by neutrophils are instead able to induce host cell damage.

**Table 1**

Gc proteins that confer resistance to neutrophils.

| Protein Name | Mechanisms of Resistance to Neutrophils | References |
|---|---|---|
| Mpg/NGO1686 | PG peptidase enhances resistance to CAMPs and ROS via presentation of type IV pili | 63, 64, 65 |
| RecN | Unclear | 64 |
| LtgA, LtgD | PG lytic transglycosylases together confer envelope integrity to defend Gc from lysozyme and neutrophil elastase; limit granule exocytosis and phagosome-granule fusion | 62** |
| TdfH | TonB-dependent transporter extracts Zn from calprotectin and enhances Gc survival in NETs | 60* |
| Nuc | Thermonuclease released extracellularly cleaves NETs | 59* |
| LptA | Phosphoethanolamine transferase for lipid A enhances Gc resistance to neutrophil CAMPs and proteases; limits phagosome-granule fusion | 35* |
| MIP | Peptidyl-prolyl isomerase protects by unknown mechanism | 39* |
| LdhA, LdhD | D-lactate dehydrogenases enhance Gc survival in neutrophils, potentially by obtaining lactate as a carbon source | 66 |
| Pili | Type IV pili protect against CAMPs and ROS | 63 |
| Lst | Sialylation of Gc N-lactotetraose-containing LOS inhibits phagocytosis by neutrophils in suspension | 67,68 |
| PorB | Essential porin inhibits the neutrophil oxidative burst | 69,70 |