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Mucosal Immunity and Evasion Strategies of *Neisseria gonorrhoeae*

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1. Introduction

Neisseria gonorrhoeae, the gonococcus, is a gram-negative diplococcus which causes the sexually transmitted disease gonorrhea (Figure 1). The contagious nature of gonococcal infection remains a major global health problem and represents 88 million new cases every year (WHO, 2011). *N. gonorrhoeae* is transmitted by human to human contact and is highly adapted to the genital tract, surviving poorly outside the human body. However, gonococcus develops resistance to antimicrobials, antigenic variability and mechanisms of immune evasion by which it evades host defenses, thus persisting and often causing undetected asymptomatic infection (Tapsall, 2001).

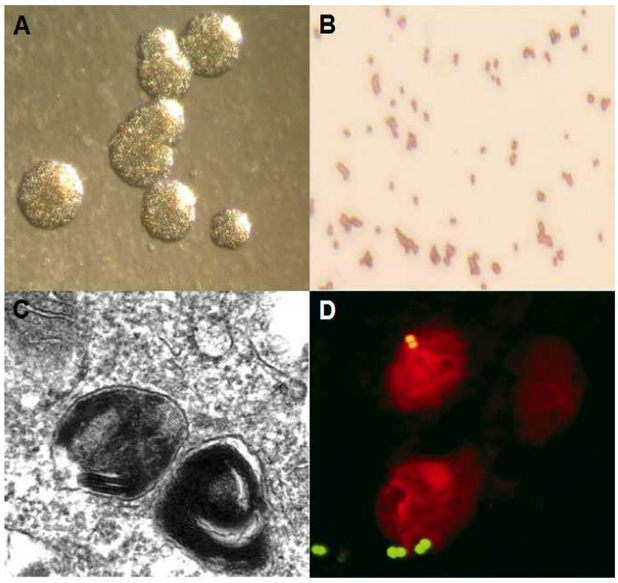

Fig. 1. *Neisseria gonorrhoeae*. (A) Colonies on agar, (B) Gram-staining, (C) Transmission electron microscopy, (D) Confocal microscopy of the bacteria (in green).

The symptoms of gonorrhoea are similar to those caused by other agents, most notably *Chlamydia trachomatis*. *N. gonorrhoeae* causes infections mainly of the urethra in men and the endocervix in women, although it may also infect extragenital mucosal sites, including the oropharynx and anorectum. Ocular infections also occur, and in neonates could cause blindness (Tapsall, 2001). Genital infection in men usually causes urethritis and epididimitis with purulent urethral exudates (Apicella et al., 1996), however an important proportion of infected men never develop symptoms and more than half of infected women develop an asymptomatic silent infection (Farley et al., 2003; Handsfield et al., 1974; John and Donald, 1978). Genital tract gonorrhea gives rise to well recognized complications including upper reproductive tract infections in women, such as pelvic inflammatory disease (PID), a condition that affects between 10% and 20% of infected women in the third world. PID encompasses a range of inflammatory conditions of the upper reproductive tract and has several potential sequelae including infertility, ectopic pregnancy, among others (Hoyme, 1990; Tapsall, 2001).

The purulent exudates produced by infected men and the cervical secretions of women with gonorrhoeae contain bacteria attached to and within polymorphonuclear leukocytes (PMNs) (Apicella et al., 1996; Ovcinnikov and Delektorskij, 1971), which are the primary innate immune responders to bacterial and fungal infection and are capable of phagocytosing and killing a variety of microorganisms (Borregaard, 2010). Yet, in spite of the numerous PMNs at the site of gonorrheal infection, viable gonococci can be cultured from the exudates of Infected individuals suggesting that the PMNS driven innate immune response to *N. gonorrhoeae* are ineffective at clearing a gonorrheal infection (Johnson and Criss, 2011). Considering further that the humoral immune response against *N. gonorrhoeae* is extremely low in serum and in secretions of the human (male and female) during infection (Hedges et al., 1999; Hedges et al., 1998), the persistence of gonococcus can be explained by the presence of an ineffective immune response which facilitates the long-term colonization of hosts, creating enhanced opportunity for dissemination and transmission of gonorrhea.

The aim of this chapter is to review advances in our understanding of the immunity against *N. gonorrhoeae* and those mechanisms of evasion that seem to be responsible for the restricted immune response frequently observed.

2. Gonococcal membrane proteins and early steps of infection

Infection of genital epithelial cells by *N. gonorrhoeae* is a multi-step process, consisting of adherence, invasion, intracellular survival and exocytosis. These events are initiated and mediated by multiple interactions between gonococcal surface molecules and epithelial cells. These interactions activate signalling cascades in host cells and trigger the reorganization of the actin cytoskeleton, which is required for the entry of the bacteria into the cells. Pilus retraction from adherent gonococci on the epithelial cell surface activates calcium flux (Ayala et al., 2005), the PI3K/Akt pathway (Lee et al., 2005) and the MAP kinase ERK pathway (Howie et al., 2008). The interaction of opacity protein (Opa) with heparin sulfate proteoglycans (HSPG) activates phosphatidylcholine-specific phospholipase C (PLC) and the acid sphingomyelinase (Grassme et al., 1997). Opa also can trigger integrin-mediated protein kinase C (PKC) activation through binding to the serum-derived extracellular matrix proteins, fibronectin and vitronectin (Dehio et al., 1998a; Dehio et al., 1998b; Dehio et al., 1998c).

2.1 Type IV pili

Although there are many potential cell surface proteins of *N. gonorrhoeae* having a role in cell-host interaction, attention of most studies has focused on a few of them. This is the case of the gonococcal type IV pili which are composed of a major structural subunit, the pilin or PilE protein, assembled into helical pilus fibers (Parge et al., 1995). *In vitro* studies indicate that antigenic variation of this protein can affect pilus-mediated adherence to human cells (Jonsson et al., 1994; Long et al., 1998; Rudel et al., 1992). The binding of *N. gonorrhoeae* pili to host cells is thought to involve the complement regulatory protein CD46 (membrane cofactor receptor) (Kallstrom et al., 2001). In fact, the association of pili with CD46 in cervical carcinoma cells results in a cytoplasmic calcium flux derived from intracellular calcium stores (Kallstrom et al., 1998). However, not all studies support this role for CD46. Accordingly, no binding of piliated gonococci was observed on CD46-transfected cells and furthermore, specific down-regulation of CD46 expression in human epithelial cell lines did not alter the binding of piliated gonococci (Kirchner et al., 2005; Kirchner and Meyer, 2005; Tobiason and Seifert, 2001). Thus the topic remains controvertial. There are other potential receptors for pili attachment, i.e., integrins containing a domain known as I-domain. Edwards et al. demonstrated that pili bind to I-domain-containing integrins on primary cell cultures derived from cervical and male urethral epithelia (Edwards and Apicella, 2005; Edwards et al., 2002). In this regard, the complement receptor 3 (CR3; integrin αMβ2 or CD11b/CD18) serves as the key receptor mediating gonococcal adherence to human cervical epithelia, *in vivo*, as well as *ex vivo* (Figure 2) (Edwards et al., 2001).

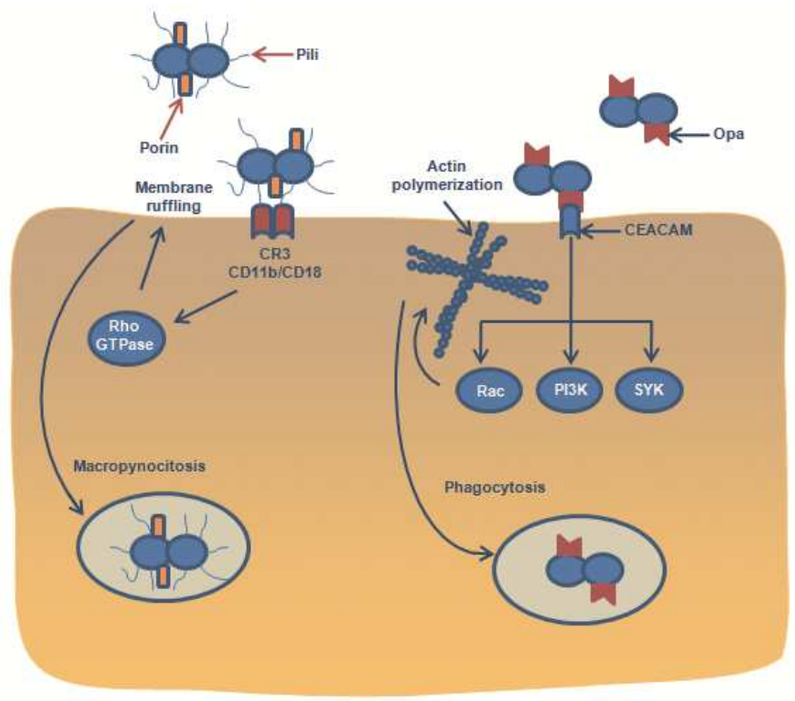

Fig. 2. Adhesion and internalization of N. gonorrhoeae in the host cell.

Pilus engagement has also been demonstrated to play a role in host cell cytoskeletal rearrangements (Edwards et al., 2000; Grassme et al., 1996; Griffiss et al., 1999; Merz et al., 1999; Merz and So, 1997). Membrane ruffles are induced in response to gonococci; epithelial cell invasion occur primarily in an actin-dependent manner, but it does not appear to require *de novo* protein synthesis by either the bacterium or the host cervical cell, eliciting substantial rearrangements of filamentous actin in the host cell cortex directly beneath sites of bacterial contact (Merz et al., 1999). Engagement of CR3 on primary cervical epithelial cells results in vinculin- and ezrin-enriched focal complex formation before membrane ruffle formation, bacteria reside within macropinosomes, and an accumulation of actin-associated protein occur in response to gonococcal infection (Edwards et al., 2000). Finally a signal transduction cascade that is dependent upon the activation of phosphatidylinositol 3-kinase or MAP kinases and Rho GTPases is activated (Edwards et al., 2001).

2.2 Opacity-associated (Opa) adhesin proteins

Opacity-associated adhesion proteins located in the gonococcal outer membrane facilitate the interaction of bacteria with a number of host cell types, including epithelial cells on mucosal surfaces and various immune cells, indicating a direct effect on the immune response. Receptor tropism of Opa proteins can be broadly divided into two categories, those that bind to members of the carcinoembryonic antigen cell adhesion molecule (CEACAM) family (Figure 2) and those that bind to HSPGs (Bos et al., 1997; Chen et al., 1995; Chen and Gotschlich, 1996; Chen et al., 1997; Gray-Owen et al., 1997a; Gray-Owen et al., 1997b; Popp et al., 1999; van Putten and Paul, 1995; Virji et al., 1999; Virji et al., 1996a; Virji et al., 1996b). These categories are represented by Opa50, i.e., Opa proteins that recognize HSPG, and Opa52, i.e., Opa proteins that recognize members of CEACAM familiy. Vitronectin and fibronectin function as required bridging molecules between the gonococcus and its target HSPG receptor(s) (Duensing and Putten, 1998; Duensing and van Putten, 1997; Gomez-Duarte et al., 1997; van Putten et al., 1998). Association with an integrin coreceptor (vß3 or vß5 for vitronectin-mediated adherence or vß1 for fibronectin-mediated adherence) triggers a signaling cascade within the target cell that is dependent upon the activation of PKC (Dehio et al., 1998c).

The binding sites of Opa proteins reside on the amino-terminal domains of the CEACAM family, which are largely conserved and therefore allow one or more Opa proteins to target distinct CEACAMs (Chen and Gotschlich, 1996; Muenzner et al., 2000; Virji et al., 1996b). As CEACAMs may contain immunoreceptor tyrosine-based inhibitory motifs (ITIMs) or immunoreceptor tyrosine-based activation motifs (ITAMs) (Hammarstrom, 1999), the consequences of downstream signaling following bacterial ligation depend on the receptor and target cell involved. From studies so far, it can be concluded that Opa–CEACAM interactions result in cellular invasion (Muenzner et al., 2000; Virji et al., 1999). The CEACAM receptor-mediated phagocytosis of Opa(52)-expressing *N. gonorrhoeae* results in a rapid activation of the acid sphingomyelinase. Furthermore, the CEACAM receptor-initiated stimulation activates a cascade via Src-like protein tyrosine kinases, Rac1 and PAK to Jun-N-terminal kinases (Hauck et al., 2000; Hauck et al., 1998).

The gonococcal opacity proteins are a well-studied example of phase-variable surface structures. Gonococcal strains express several antigenical distinct Opa proteins that are encoded by separate chromosomal alleles (Bhat et al., 1991; Connell et al., 1990; Dempsey et

al., 1991). Each *opa* gene undergoes phase variation via frameshift mutations that cause changes in pentameric repeats in the *opa* structural gene (Murphy et al., 1989). Bacteria that express no Opa proteins, bacteria that express one Opa protein, and bacteria that express multiple Opa proteins simultaneously result from these reversible mutations. This is one of the earliest described mechanisms of immune evasion found in gonococcus.

2.3 Porin, the outer membrane protein channel

Porin, is membrane channel through which small molecules traverse the gonococcal outer membrane, is thought to play multiple roles in potentiating disease caused by *N. gonorrhoeae*. Porin molecules trigger different responses within host cells depending upon the particular porin and the host cell type. A feature of gonococcal porin is its ability to translocate into eukaryotic cell membranes (Lynch et al., 1984; Weel and van Putten, 1991), where it acts as voltage-gated channel that is modulated by host cell ATP and GTP (Rudel et al., 1996). It has also been demonstrated that *N. gonorrhoeae* infection of epithelial cells results in selective porin transport to the mitochondria (Muller et al., 2000; Muller et al., 2002). Within the cell mitochondrial membrane, porin initiates apoptosis by inducing a calcium influx and, consequently, calpain and caspase activity within these cells (Muller et al., 1999). In contrast to the porin-induced apoptosis observed in HeLa cells, gonococcal infection of primary human male urethral epithelial cells results in antiapoptotic events (Binnicker et al., 2003; Binnicker et al., 2004). Finally, porin also acts as an actin-nucleating protein in epithelial cells (Wen et al., 2000) facilitating the cytoskeletal rearrangements required for actin-mediated entry of the gonococcus into its target host cell.

2.4 Lipooligosaccharide (LOS)

Lipooligosaccharide is a major antigenic and immunogenic component of pathogenic *Neisseria* species. LOS produced by these bacteria consists of an oligosaccharide (OS) moiety and lipid A, and structural variation of the OS leads to LOS heterogeneity (Preston et al., 1996). Studies using primary male urethral epithelial cells demonstrated an association between the urethral epithelium and the gonococcus through the interaction of the asialoglycoprotein receptor (ASGP-R) and gonococcal LOS (Harvey et al., 2001). In primary cell culture, engagement of the ASGP-R by the gonococcus results in pedestal formation beneath the bacterium (Harvey et al., 1997). Pedestal formation is also observed in microscopic analysis of exudates collected from men with naturally acquired gonococcal urethritis (Apicella et al., 1996; Harvey et al., 1997). Evidence suggests that endocytosis occurs primarily by actin-dependent (Giardina et al., 1998) and clathrin-dependent processes (Harvey et al., 1997).

3. Immune response against *N. gonorrhoeae*

The immunity against bacterial infections is achieved by many levels of defense that are triggered depending on the type, number and virulence of the bacteria that enter to the body (Figure 3). If the infection is mild, the tissue phagocytes are able to kill the bacteria in the phagolysosomes by reactive oxygen and nitrogen intermediates and proteolytic enzymes. In addition, these cells are able to secrete pro-inflammatory cytokines such as interleukin (IL)-1, IL-6, IL-8 and Tumoral Necrosis Factor (TNF) which initiates

inflammatory response. On the other hand, antigen processing and presentation, which is a crucial biological process for the initiation of adaptative immune response, might initiate antigen-specific immune response and a long lasting memory. Dendritic cells (DCs) are a subgroup of high-power antigen presenting cells (APC) with a unique ability to attract and interact with naive T cells to induce a primary immune response (Sabatos et al., 2008; Verhagen et al., 2008). Immature DCs (iDCs) reside in most peripheral tissues where they act as sentinels for incoming pathogens (Rowell and Wilson, 2009). After exposure to pro-inflammatory cytokines and microbial products, iDCs undergo a process termed maturation, which involve up-regulation of MHC molecules, co-stimulatory molecules, secretion of pro-inflammatory cytokines and migration to draining lymph node where mature DCs activate T cells (Xu et al., 2007). Following antigen stimulation by DCs, T cells begin an expansion process, as a result of extensive division. Under a control of DCs, helper T cells (Th) acquire the ability to respond to infection through the production of powerful cytokines like interferon gamma (IFN-γ), which is able to activate macrophages resisting infections by facultative and obligate intracellular microbes (Th1 cells) (Napolitani et al., 2005), or IL-17, which mobilize phagocytes at body surfaces to resist extracellular bacteria (Th17 cells) (LeibundGut-Landmann et al., 2007). Th17 cells represent a distinct lineage that originates mainly in the presence of TGF-β1 and IL-6 and need the presence of IL-23 for their expansion and/or maintenance (Annunziato et al., 2007). IL-23 is secreted by macrophages and DCs in response to microbial products and inflammatory cytokines (Langrish et al., 2004). Once differentiated, Th17 cells are able to secrete preferentially IL-17A, IL-17F and IL-22, a particular set of cytokines not secreted by the other Th cells (Ouyang et al., 2008). IL-17 plays a particularly significant role in regulating neutrophils (PMNn) recruitment and granulopoiesis via the production of IL-8 and MIP-2 (CXCL2) (Laan et al., 1999). In early stages of infections, interactions between *N. gonorrhoeae* and epithelial mucosa trigger immune response with release of IL-1, IL-6, IL-8 and TNF which serve to recruit and activate PMNn to the site of infection and promoting their bactericidal activity limiting bacterial penetration into submucosal tissues (Fisette et al., 2003; Maisey et al., 2003; McGee et al., 1999). In men, PMNs appear in urethral swabs and urine several days after infection and immediately prior to the onset of symptoms (Cohen and Cannon, 1999). In women with gonorrhea, the cervical secretions also contain PMNn (Evans, 1977) and bacteria are attached to and within PMNn (Johnson and Criss, 2011). In spite of the numerous PMNn at the site of gonorrheal infection, viable gonococci can be cultured from the exudates of infected individuals (Wiesner and Thompson, 1980). When bacteria crosses the layer of epithelial cells, obtaining access to submucosa, they have the first encounter with macrophages and DCs (Rarick et al., 2006). DCs interaction with *N. gonorrhoeae* surface factors like Pili and Opa is mediated by members of the CD66 family, CD46 and CR3. However, C-type lectins (macrophage galactose-type lectin -MLG- and DC-SIGN) constitute the main DCs expressed receptor for *N. gonorrhoeae* (Astier et al., 2010).

Most studies that have investigated antigonococcal immune responses have focused predominantly on humoral responses (Table 1). The hallmark of humoral immune response against *N. gonorrhoeae* is the extremely low levels of anti-gonococcal antibodies found in serum and secretions of the human (male and female) during infection (Hedges et al., 1999; Hedges et al., 1998), indicating that humoral immunity against gonococcus is highly limited (Hedges et al., 1999; Song et al., 2008). Antigenic heterogeneity is a major consideration for humoral immunity in gonococcal infection studies. Meanwhile Pili, protein I (PI), protein II

(PII), H.8, IgAl protease and LOS are quantitatively the most important antigens in generating antibody responses in gonococcal infection. It is clear that patients make antibodies against the pili of the infecting gonococcal strain. In women, pili appeared to be the predominant antigen in the immune response unlike men, that have higher levels of antibodies to other antigens than pili (Brooks and Lammel, 1989). Thus, antibodies generated are directed against other major membrane molecules, such as Opa proteins and Porin protein (Brooks and Lammel, 1989; Hedges et al., 1999; Hedges et al., 1998; Plummer et al., 1993; Plummer et al., 1994; Zheng, 1997). Although some of these have bactericidal activity, they are not protective and seem to be blocked by immunoglobulins against the outer membrane protein 3 (RmP). In fact, women with these antibodies were at increased risk to gonococcal infection (Plummer et al., 1993). The absence of induction of humoral response results on limited or no protection against re-infection with *N. gonorrhoeae* despite the generation of serum antibody responses against antigens produced by several prototype gonococcal vaccines (Boslego et al., 1991; McChesney et al., 1982; Tramont et al., 1981).

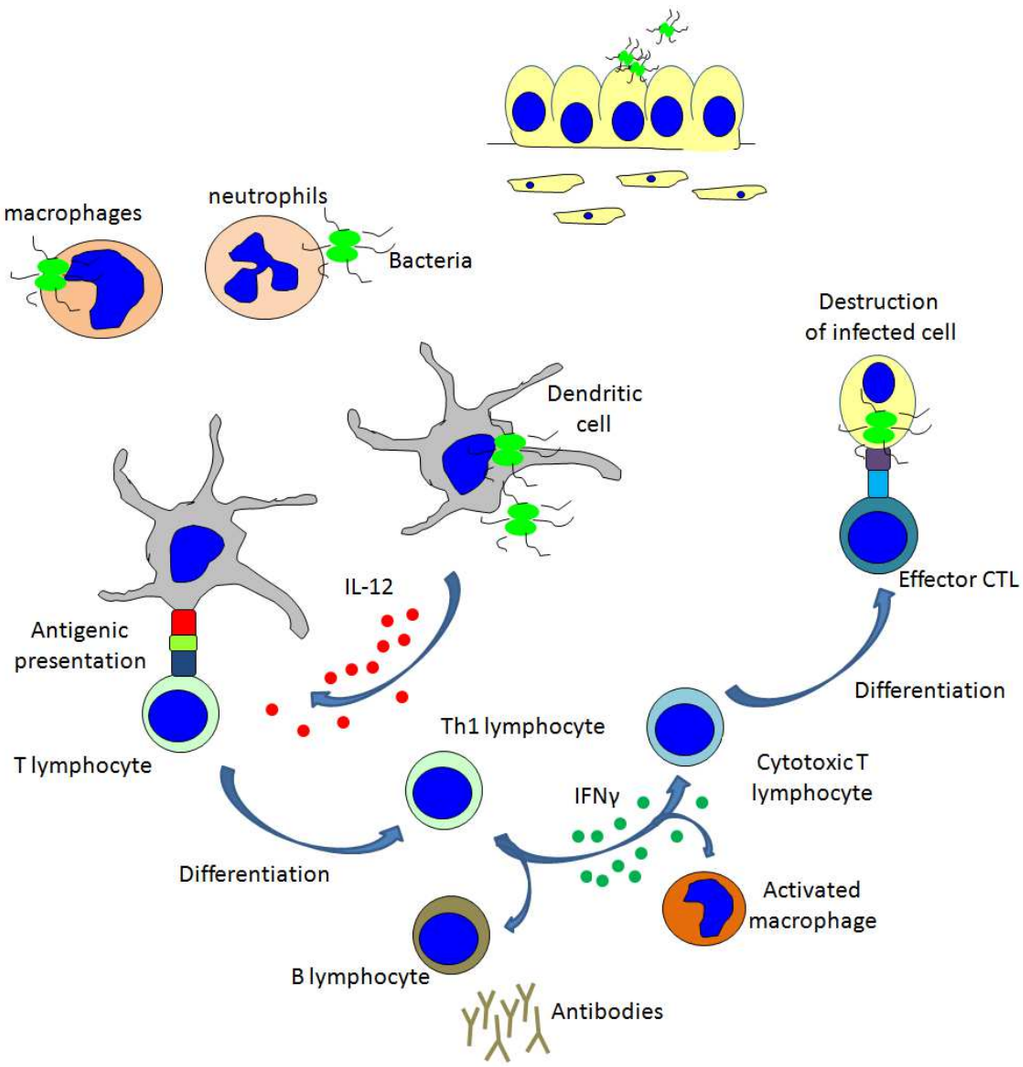

Fig. 3. Protective immune responses against intracellular bacteria.

Antigen	Effects on immune response	References
N. gonorrhoeae	IgG>IgM and sIgA>IgA	(Tapchaisri and Sirisinha, 1976)
Outer membrane protein I	IgA>IgG	(Jeurissen et al., 1987)
Outer membrane protein I	IgA>IgG	(Kohl et al., 1992)
Porin	Up-regulated B7-2 expression of B lymphocytes	(Wetzler et al., 1996)
Heat labile and fixed *N. gonorrhoeae*	IgG>IgA>IgM serum	(Cohen, 1967)
Pili and outer membrane protein II	IgG serum	(Lammel et al., 1985)
Outer membrane protein II	IgA serum	(Lammel et al., 1985)
Outer membrane protein I and II and pili	IgG and IgA vaginal fluid	(Lammel et al., 1985)
LPS	IgG>IgA in serum	(Ison et al., 1986)
Outer membrane protein III	IgG in serum	(Rice et al., 1986)
N. gonorrhoeae MS11	Slight increase of IgG and IgA in serum	(Hedges et al., 1999)
N. gonorrhoeae mice infection	Increased of neutrophils and macrophage in site of infection	(Song et al., 2008)
N. gonorrhoeae mice infection	IgG>IgA>IgM in vaginal fluid	(Song et al., 2008)
Whole-protein extractes of *N. gonorrhoeae* P9-17	Low titers of IgG in serum	(Imarai et al., 2008)
N. gonorrhoeae	Th17 profile immune response and increased IL-17	(Feinen et al., 2010)
IgA1 protease	Th1 pro-inflammatory profile with increased IFNγ and TNFα	(Tsirpouchtsidis et al., 2002)
IgA1 protease	IL-1β, IL-6, TNFα and IL-8	(Lorenzen et al., 1999)
Porin	Th2 pro-inflammatory profile with increased of IL-4	(Simpson et al., 1999)
Porin	B lymphocytes activation and up-regulation of CD40	(Snapper et al., 1997)
Pili	Activation and proliferation of $CD4^+$T Lymphocyte	(Plant and Jonsson, 2006)
Opa	Arrest of activation and proliferation of $CD4^+$ T lymphocytes binding CEACAM1	(Boulton and Gray-Owen, 2002)

Table 1. Anti-gonococcus immune responses.

Similarly, in the murine model of infection, no antibody induced response has been detected. In Balb/c mice, *N. gonorrhoeae* is able to reach the upper genital organs and to invade uterine tissue, as it occurs in humans (Imarai et al., 2008; Jerse, 1999). Interestingly, studies in this model revealed several features of infection that mimic a good spectrum of the characteristics of the human disease. Some of them seem highly valuable, (i) the bacteria introduced in the vagina not only invade and colonize the lower genital tract, but also spread to the upper organs (uterus and oviducts) (Inaba et al., 1992), (ii) infection occurs with no signs of the disease, just as it occurs in a high percentage of women during natural infection (Farley et al., 2003; Inaba et al., 1992) and (iii) the bacteria remains alive within the internal compartments of the infected cells, invading uterine tissues up to 22 days post inoculation (Imarai et al., 2008).

On the other hand, CD4+ T cell responses also occur with gonoccocal antigens. Antigenic stimulation with Porin induces an increase in the percentage of IL-4 producing CD4+ T cells, but no production of other cytokines such as IL-2, IL-10, IFN-γ, or TNF occurs, indicating that infected individuals produce a Th2 response against Porin (Simpson et al., 1999).

Moreover, gonococcal pili interaction with CD4+ T cells induces the activation and proliferation of lymphocytes and stimulates the secretion of IL-10 (Plant and Jonsson, 2006). In contrast, Opa proteins mediate binding to CEACAM-1 expressed by CD4+ T cells and suppress activation and proliferation of naive lymphocytes (Boulton and Gray-Owen, 2002; Lee et al., 2008). Rarick et al. showed a differential activation of peripheral blood mononuclear cells by *N. gonorrhoeae* that includes the early induction (96 hours) of IL-2, IL-12 and IFN-γ (Th1 cytokines), IL-4 (Th2 cytokine), IL-10 (immunosuppressive cytokine) and MCP-1, MCP-2 (chemotactic cytokines). The cytokine response observed in this study indicate that distinct gonococcal components produce antagonistic signaling and cytokines suggesting that *N. gonorrhoeae* infection cannot be initially categorized as Th1 or Th2 response (Rarick et al., 2006). Recent studies in the murine model of gonococcal genital tract infection showed that Th17 cells are involved in the immune response to *N. gonorrhoeae*. This response leads to IL-17 dependent secretion of IL-6, LIX and MIP2α and subsequent recruitment of PMNn, which is delayed in the presence of IL-17A blocking antibodies or deletion of IL-17RA prolonging infection (Feinen et al., 2010).

Overall, most known gonococcal antigens are able to induce humoral and cellular immune responses in the human, but a protective immune response has not been identified. Data suggest that the bacteria have mechanisms to evade destruction by PMNn, antibodies and T cells.

4. Mechanisms of immune evasion by *Neisseria gonorrhoeae*

Several studies suggest the promotion of direct inhibitory mechanisms by gonococcus to escape the immune response. Data indicate that bacteria induces transient reduction of CD4+ and CD8+T cells during acute gonococcal infection in HIV-1-positive woman, with increase in plasma HIV-1 RNA copy number and plasma concentration of IL-4, IL-6, IL-10 and TNF-α soluble receptor (Anzala et al., 2000). Gonococcal infection also correlates with suppression of activation and proliferation of CD4+ T lymphocytes (Boulton and Gray-Owen, 2002). In this respect, inhibitory effect is mediated by the ligation of gonococcus membrane component Opa52 present in blebs of outer membrane (OMV) to CEACAM1 (also known as CD66a or BGP) on lymphocyte (Lee et al., 2007). The interaction triggers the

phosphorilation of the ITIM impeding the normal expression of early activation marker CD69 and the subsequent proliferation of T cells. This strategy represents an effective means by which to create a "zone of immunosuppression" surrounding the infected site (Lee et al., 2008). Opa-CEACAM1-induced immunosuppression might also control the development of a humoral response, decreasing the T cell help for B cell activation or targeting the CEACAM1-expressing B cells causing cell death (Pantelic et al., 2005) and subsequent inhibition of antibody production.

On the other hand, piliated gonococci enhances T-cell activation and proliferation, regardless of whether this is mediated by the pilus itself or is due to the act of binding to a pilus receptor such as CD46 or integrins. Upon pili-CD46 ligation, the IL-10-secreting type 1 regulatory T (Tr1) cells are elicited (Plant and Jonsson, 2006). Tr1 cells are able to suppress the activation of bystander T cells via induction of IL-10 (Jonuleit et al., 2001). In addition, IL-10 suppresses the production of pro-inflammatory cytokines thereby inhibiting the ability of APC to induce differentiation of Th1 cells, just the type of response associated to protection against intracellular pathogens such as gonococcus (McGuirk et al., 2002).

In regard to the role of regulatory T (Treg) cells, we showed that in Balb/c, the mouse model of gonococcus infections, *N. gonorrhoeae* induces transforming growth factor β1 (TGF-β1)+ $CD4^+$ T cells in the mucosal lymph nodes, including a subset of CD25+Foxp3+ Tregs, indicating that type of response may avoid the host mechanisms of protection (Imarai et al., 2008). Mature CD4+ CD25- T cells can be converted in Treg cells in peripheral tissues under immunosuppressive conditions, such as exposure to IL-10 or TGF-β1 made by antigen presenting cells (Sakaguchi, 2004). Treg cells inhibit the function of effectors T cells through the secretion of suppressive cytokines IL-10 and TGF-β1, or by a cell contact-dependent mechanism via CTLA4 or GITR molecules (Bending et al., 2009; O'Connor et al., 2008; Sakaguchi, 2004). Considering that, the source of TGF-β1 could be stromal and epithelial cells of reproductive organs (Nocera and Chu, 1995; Srivastava et al., 1996; Taylor et al., 2000), which are target of gonococcus infection, it is possible that the cytokine milieu found in reproductive tract subsidized the inductions of Tregs by *N.gonorrhoeae.* In fact, we must consider that the genital tract is an immune-privileged site with expression of regulatory cytokines which might induce a tolerogenic response against gonococcus (Nocera and Chu, 1995; Srivastava et al., 1996; Taylor et al., 2000). For instance, epithelia and stromal cells of the reproductive organs of the mouse and human, express high levels of TGF-β1 and other molecules involved in conditioning immune privilege sites (Chegini et al., 1994; Grant and Wira, 2003; Jin et al., 1992; Wada et al., 1996). Moreover, antigen presenting cells such as macrophages and DCs, regularly present in the reproductive tissues might also contribute to regulatory response, since they could promote T regulatory cells differentiation trough production of IL-10 and TGF-β1 after infection (Givan et al., 1997; Stagg et al., 1998).

The effects of interaction of different stable gonoccocal LOS phenotypes with human DCs were evaluated (van Vliet et al., 2009). Interestingly, this study revealed that LOS variants result in alterations of cytokine secretion profiles of DCs and in the induction of distinct adaptive CD4+ T helper responses. Gonococcus significantly increased IL-10 production, as well as pro-inflammatory cytokines, such as TNF-α, IL-6, IL-8 and IL-12. However, only IL-10 production was modulated by LOS variation. Supporting the anti-inflammatory or regulatory effects of gonococcus on APCs, recently we found that the bacterium was unable to induce significant up-regulation of cell surface co-stimulatory molecule CD86 in

macrophages, as well in DCs (unpublished data). This suggests that, although *N. gonorrhoeae* is actually phagocytosed by macrophages and DCs, the bacteria can deteriorate antigen presenting function. Moreover, gonococcus was unable to induce up-regulation of MHC class II in macrophages, this molecule is involved in antigen processing and presentation, therefore this implies that macrophages do not have a proper antigen presenting function. In addition, gonococcus induced IL-10 and TGF-β1 in dendritic cells reaching an anti-inflammatory or regulatory response.

Altogether, studies so far show that *N. gonorrhoeae* might control immune response by inducing (1) suppression of activation and proliferation of CD4+ T lymphocytes, (2) secretion of tolerogenic-type cytokines, (3) inhibitory T cells (Tr1 and Tregs), and (4) by deteriorating antigen presenting function. This wide variety of immune evasion mechanism may explain the frequent appearance of persistent and asymptomatic infection (Figure 4).

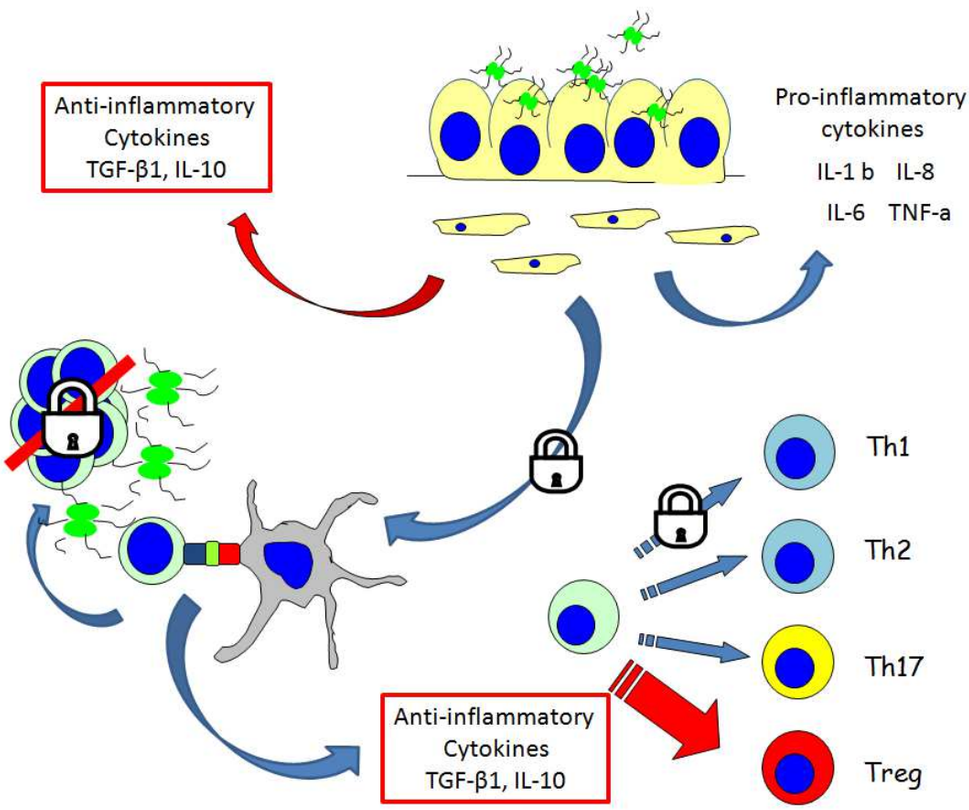

Fig. 4. *N. gonorrhoeae* interferes with immune responses.

5. Conclusion

Neisseria gonorrhoeae infects the reproductive tract of the human causing gonorrhea. Mechanisms of infection involved the early attachment of gonococcal membrane components, such as Pili, Opa, Porin and LOS, to cell host receptors. Frequently, the bacteria develop persistence and asymptomatic disease, which seem to be associated to the gonoccoccus ability to evade immune response. Several lines of research revealed that *N.*

gonorrhoeae is able to subvert polymorphonuclear cell phagocytic destruction, induces a weak humoral immune response, decreases antigen presenting properties of macrophages and dendritic cells, inhibits T cell proliferation and induces anti-inflammatory cytokines and T inhibitory cells. On the whole, this seems to be a complex network of immune evasion mechanisms responsible for the restricted immune response frequently observed during gonococcal infection.

6. Acknowledgment

We thanks the support of DICYT 021043IB, PBCT to CA and CONICYT Fellowship to KM and SR.

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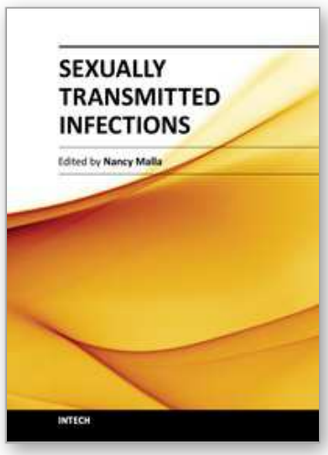

Sexually Transmitted Infections

Edited by Prof. Nancy Malla

ISBN 978-953-51-0258-8
Hard cover, 244 pages
Publisher InTech
Published online 21, March, 2012
Published in print edition March, 2012

Sexually transmitted infections (STIs) are infections that are spread primarily through person to person sexual contact. There are more than 30 different sexually transmissible bacteria, viruses and parasites. STIs lead to high morbidity and complications. This book entitled as Sexually Transmitted Infections is not a text book but provides useful information for general reference work for physicians, researchers and students interested in the subject. Each chapter is abundant in tips useful to general readers as well. It also includes the Introductory chapter providing an overview with special emphasis on syndromic approach to the management of STIs in clinical setting.

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