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by sari simanjuntak

Submission date: 11-Dec-2023 11:02AM (UTC+0700)
Submission ID: 2255068769
File name: Suryowati1532023AJBGMB108493.pdf (242.58K)
Word count: 5407
Character count: 31041

Asian Journal of Biochemistry, Genetics and Molecular Biology

Volume 15, Issue 3, Page 82-90, 2023; Article no.AJBGMB.108493
ISSN: 2582-3698

Neisseria Gonorrhoeae: Its Dominant Properties to Establish Contact and Attachment that Facilitate Epithelial Invasion and Colonization From a Biochemist Perspective

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Author's contribution

The sole author designed, analysed, interpreted and prepared the manuscript.

Article Information

DOI: 10.9734/AJBGMB/2023/v15i3341

Open Peer Review History:
This journal follows the Advanced Open Peer Review policy. Identity of the Reviewers, Editor(s) and additional Reviewers, peer review comments, different versions of the manuscript, comments of the editors, etc are available here: https://www.sdiarticle5.com/review-history/108493

Review Article

Received: 24/08/2023
Accepted: 31/10/2023
Published: 02/11/2023

ABSTRACT

Aim: to discuss recent epidemiology of gonorrhoea and updates regarding its pathogenesis with a focus on biochemical aspects of contact and adhesion that preceded its epithelial invasion.
Discussion: *Neisseria gonorrhoeae*, a Gram-negative obligate human pathogenic bacterium, infects human epithelial cells and causes sexually transmitted diseases in both males and females Gonorrhea rates are rising in many countries. It could lead to long-term health problems and even infertility. Vulnerable groups including men who have sex with men and sex workers appear to bear disproportionate burdens of gonorrhea. As *N. gonorrhoeae* advances through the steps of disease formation and pathogenesis (transmission, adherence, colonization and invasion, and also immune evasion), the bacterium expresses some virulence factors to facilitate its survival and replication; while at the same time keeping its existence barely invasive and almost undiscoverable by active immune cells. Adherence to epithelial cells becomes the first event that precedes invasion.

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Conclusion: Adhesion of gonococci to mucosal epithelial cells appears to be a critical step in the pathogenesis of gonococcal infection. Gonococci can adhere to a variety of human cells. Gonorrhea has multiple surface proteins that facilitate adhesion. N. gonorrhoeae utilize type IV pili and Opa, opacity-associated proteins, surface proteins involved in cellular attachment that preceded its invasion, Lipooligosaccharides (LOS) and also the outer membrane protein porin (POrB).

Keywords: Mucosal; microcolonies; type IV pili; conserved hydrophobic N terminus; Opa protein; lipooligosaccharide; porin.

1. INTRODUCTION

Neisseria gonorrhoeae is responsible for causing gonorrhea, a sexually transmitted infection which has been reported to infect humans since ancient times [1]. It is a well-adapted organism that able to overcome the already existing normal microbiome [2], having an awesome ability to accommodate the harsh internal condition of their human host [3] and has maintained ways to evade the host immune properties [4]. Its initial predilection is mainly shallow or restricted near the surface, namely the epithelial mucosa of the female endocervix [5]. Colonization and disruption of the epithelium is actually an important route of infection used by this mucosal pathogens [6]. The normal epithelium actually neutralizes invasion by managing to exfoliate damaged portion of the affected cells while keeping the best mucosal barrier in business [7].

Over the past decade, extensive studies of N. gonorrhoeae have shown that in media containing glucose [8], the compound lactate (a classical byproduct of glucose metabolism) actually encourages the bacteria's metabolism [9], and even ensuring its survival inside the human polymorphonuclear leukocytes [10]. These properties could improve its colonization [11], increased lipopolysaccharide synthesis [12], increase gonococcal resistance to complement-mediated killing by human serum [13] and also contributes to antibiotic resistance [14]; or in other wors lactate play a central role in N. gonorrhoeae pathogenicity. Lactate and glucose are present together in most sites where infection and active inflammation occurs *In vivo* [15]. This mini-review describes the gonococci dominant properties to establish contact, attachment, epithelial invasion and colonization from a biochemist perspective.

2. EPIDEMIOLOGY AND PATHOGENESIS OF *N. Gonorrhoeae*

By the year 2020, the WHO roughly estimated 82.4 million new STIs due to N. gonorrhoeae among adults aged 15 - 49 years old, globally [17]. Prevalence of gonorrhoea is highest among specific populations such as men who have sex with men [18], sex workers [19], transgender individuals [20] and adolescents and young people in high burden countries [17]. Gonorrhoea prevalence in infertile sub populations is several folds higher than in the general sub population, with even higher prevalence in sub population of women suffer from tubal factor infertility and in people with secondary infertility [21]. These allegations contribute the potential role of gonorrhoea in causing infertility and indicate that some type of infertility is very likely preventable by means of preventing gonorrhoea transmission [22].

The main obstacles for portraying its pathogenesis are include its all-in exclusive human host [23] and in combination with its active and continuously modifying superficial sector [24]. Its primary niche is in the surface portion of human internal genital organ [3]. While N. gonorrhoeae infects both sexes (men and also women), most commonly manifests as urethritis in men and cervicitis in women [25]. Unfortunately for female patients, silent but active infection tends to develop more intricated consequences, ranging from simple colonization without any distinct clinical appearance [26] to a more severe clinical conditions such as pelvic inflammatory disease [27], ectopic pregnancy [28] and tubal infertility [22,28]. Unfortunately, due to the larger part of infections among female group are asymptomatic [26], this condition gives the bacteria the privilege to escalate silently, until then these microorganisms reach deeper anatomical structures and cause more serious problems with more prominent symptoms; a condition called complications. Even though a study conducted by Teker et al [29] revealed a significant proportion of asymptomatic female patients somehow able to unloaded their infections spontaneously.

The integrity of the vaginal epithelium is crucial for women's reproductive health and for providing protection against sexually transmitted infections and even HIV [30]. The surface of entire female reproductive tract coated with a variety of epithelial cells [31-35]. Neisseria gonorrhoeae adheres for the first time to the urogenital tract surface by attaching to surface structures namely epithelium. This microorganism using at least four structure to facilitate their attachment, namely: (1) Type IV pili (Tfp) [33,35-37], (2) opacity (Opa) proteins, (3) Lipooligosaccharide (LOS), or (4) outer membrane protein porin (PorB) and all of these four, together and simultaneously, arbitrate the complex interactions between N. gonorrhea and epithelial cells or phagocytes subsequent to adhesion [32,33].

3. BIOCHEMICAL ASPECTS OF CONTACT AND ATTACHMENT

Major infection mechanism of any mucosal pathogens actually involved the combination of colonization and perturbation of the epithelium at the surface of organ [38-46]. The epithelium neutralizes infection by suddenly shedding all broken epithelial cells while keeping the most important function of mucosal, named barrier [39,40,47].

Vaginal epithelium is actually inhabited by diverse strains and species of microorganisms considered as normal microbiota [2]. The bacterial composition of vaginal microbiota controls the balance between bacteria and yeast, or in simplified word the equilibrium between health and disease. There must be at least relative endowment of the epithelial cell combine with bacterial cell surfaces regarding to its adhesion, that according to Ferrari et al [48] there is also influence of surface properties, and in addition to that whether and how adhesion is controlled due to certain cell membrane portions [49]. The forces that facilitate Bacterial adhesion combine with the portion affected (cell membrane regions) which was not located above the nucleus are actually bind better compare to regions located above the nucleus; this condition apply to all inhabited organism whether pathogens or commensal and probiotic organism such as Lactobacillus strains that actually implicated in maintaining health condition.

One must kept in mind that, adhesion force ratios over certain membrane regions abroad from and upward the nucleus happen at the same time with the ratios between the amount of attaching microorganism over both portion of the infected regions [50]. Bacterial adhesion forces were dramatically decreased by depleting the epithelial cell membrane of cholesterol [51] or sub-membrane cortical actin [52]. Pathogenic obligate intracellular organism use principally host-derived structures to facilitate its movement through (and also between) cells [53]. Epithelial cells actually have the authority to regulate affected membrane regions to which bacterial adhesion is prevented, very likely to secure the nucleus and maintain its function [47].

Infection of the genital mucosa initiate by N. gonorrhoeae entail contact, adherence to and invasion of epithelial cells which preceded colonization [34]. Early bonding of gonococci to the columnar epithelial cells is helped by type IV pili [54] constructed from pilin subunit PilE proteins [55] and pilus tip-associated PilC proteins [56]. Type IV pili are composite structure in the form of long fibers that are assembled by polymerization of a major pilin protein in the periplasm of a wide range of bacteria and archaea. Type IV pili are distinctive dynamic filaments at the surface of many bacteria that can rapidly extend and retract and withstand strong forces. They play crucial roles in pathogenesis, DNA transformation, self-agglutination, proficiency for natural transformation, and twitching/spasm type motility and also are capable of rapid retraction, generating powerful motor forces [53].

In the context of adherence properties of N. gonorrhoeae, type IV pili consists of multifunctional polymers of the major pilin protein, which share a conserved hydrophobic N terminus that is a curved extended α-helix, α1, in X-ray crystal structures. Type IV pili plays an important role, that as a Gram-negative causative agent of gonorrhea, to attach to the specific epithelial cells and actively determine the colonization process [55,56]. Type IV pili-mediated gonococcal attachment [59] not directly related to pilin subunit protein PilE but by choice is prefer to be compatible with the expression of the PilC protein, which actually less profuse; and this copurifies with type IV pili. An almost identical system seems to work for the highly related species that come from the same ancestor named N. meningitides [60,61].

Gonococcal attachment is also facilitate and strengthen by the utterance of phase-variable opacity-associated (Opa) proteins [6,7,57,58].

Opa proteins are specific Gonococcal's variable outer membrane proteins that facilitate closed host-pathogen interaction; it account for the cell tropisms demonstrated by N. gonorrhoeae, e.g., for human leukocytes and epithelial cells [61, 63]. Its extensive exploration have successfully allowing researchers to reveal recognition of different host receptors responsible for attachment and also organizing the certain cell pattern tropism advertised by this bacteria, including epithelial and neutrophils [57,58] and this action being defined by precise adhesin-receptor interactions [61,62].

Lipooligosaccharide (LOS) also contribute to adherence ability [12,63,64]. This sugar is the main constituent within the outer membrane. Beside adherence, LOS also contributes in pathogenesis by arousing the host inflammatory reflex and also permiting evasion of the initially aroused host's innate immunity by way of sialylation [65]. A naturally occurring variation of the terminal carbohydrates on the lipooligosaccharide (LOS) molecule correlates with altered disease states [12, 63-65].

Biochemically, Neisserial LOS molecules constructed from hexa-acylated lipid A, two keto-deoxyoctulosonate, a carbohydrate (KDO) molecules, and one or more carbohydrate chains of 8–12 saccharide units, the core oligosaccharide; with all the three oligosaccharide chains attached to a lipid A core [66]. The oligosaccharide chains of LOS are almost identical both in sequence and linkage with the oligosaccharides expressed on the surface of human cells [63]. The synthesis of these compounds requires a series of glycosyl transferases. Besides their highly conserved core structures, the terminal oligosaccharides of LOS molecules undergo rapid phase variation 64]. LOS variation is mediated by a change in the number of guanines in the middle of the coding sequences of several key enzymes, which results in alterations in the expression of these glycosyl transferases and the surface expression of various LOS isoforms. At any given time, several LOS structures with varying terminal oligosaccharides may also be pronounced on the part of N. gonorrhoeae outer membrane. Due to its strain based variability, it has been difficult to study the structure and function of LOS. The asialoglycoprotein receptor is also expressed in human urethral epithelial cells. Neisserial LOS has a relative paucity of glycosylation when compared to lipopolysaccharide of enteric Gram-negative species. Variations in gonococcal LOS are largely due to phase-variable expression of genes involved in LOS biosynthesis, which determine core oligosaccharide structure and lst, which determines LOS sialylation.

Last but not least, the outer membrane protein porin (POrB) of N. gonorrhea. The major outer membrane porin (PorB) expressed by *N. gonorrhoeae* plays multiple roles during infection, in addition to its function as an outer membrane pore [67]. PorB is a voltage-gated pore that mediates ion exchange between *N. gonorrhoeae* and the environment and is essential for bacterial viability, likely due to its ability to allow nutrients access to the periplasm [68]. Porin is found in the outer membrane as a homotrimeric β-pleated barrel; each monomer is 32 to 35 kDa and consists of 16 transmembrane-spanning segments and 8 extracellular loops. *N. gonorrhoeae* strains contain a single porB gene in one of two allelic forms (P.IA or P.IB), and the two alleles have been associated with different biological phenotypes [67,68]. P.IA-expressing strains tend to be associated with disseminated disease, whereas P.IB-expressing isolates typically cause localized urogenital infections. There is 80% nucleotide sequence similarity between P.IA and P.IB, and the majority of the variation between alleles and between different isolates expressing the same allele occurs within the extracellular loops

In the context of *N. gonorrhea*, the known target receptors are being explored and the potential role of receptor modulation in increasing host susceptibility to infection is always be considered and perhaps become the major focus in future study. Not to mention the problem of administering drugs in the realm of limitations in terms of the drug, the host and also the gonococcal [69,70]. Most bacteria, commensal or pathogenic, actually while associating with their hosts produce certain specific adhesive molecules superficially. This molecules promotes reciprocation with surface receptors of their host or with available soluble macromolecules. Even though bacterial contact and then followed by attachment to superficial lining made by epithelial cells may be beneficial for bacterial colonization, adhesion may also causing potential harm because attachment to waken immune cells can simplify the process of phagocytosis and elimination. Certain pathogenic microorganisms have deciphered this difficulty by way of releasing an antiphagocytic surface substance that isa usually always made from polysaccharide and alternatively by expressing

their adhesins on polymeric structures that extend out from the cell surface. This is certainly an interesting topic, related to the virulence of *N. gonorrhea*, to be explored in the future.

4. CONCLUSION

Adhesion of gonococci to mucosal epithelial cells appear to be a critical step in the pathogenesis of gonococcal infection. Gonococci have the ability to adhere to a variety of human cells. Gonorrhea has multiple surface proteins that facilitate adhesion. N. gonorrhoeae utilize type IV pili and Opa, opacity-associated proteins, a surface proteins involved in cellular attachment that preceed its invasion.

COMPETING INTERESTS

Author has declared that no competing interests exist.

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