Available online at www.sciencedirect.com

ScienceDirect

Biomedical Journal

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

Review Article: Special Edition

Trichomoniasis immunity and the involvement of the purinergic signaling

Dr. Tiana Tasca

*Camila Braz Menezes, Tiana Tasca**

Parasitology Research Laboratory, Pharmacy Faculty, Federal University of Rio Grande do Sul, Brazil

ARTICLE INFO

Article history:
Received 1 March 2016
Accepted 30 June 2016
Available online 21 September 2016

Keywords:
Trichomoniasis
Innate immune response
Adaptive immune response
Evasion mechanisms
Purinergic signaling

ABSTRACT

Innate and adaptive immunity play a significant role in trichomoniasis, the most common non-viral sexually transmitted disease worldwide. In the urogenital tract, innate immunity is accomplished by a defense physical barrier constituted by epithelial cells, mucus, and acidic pH. During infection, immune cells, antimicrobial peptides, cytokines, chemokines, and adaptive immunity evolve in the reproductive tract, and a proinflammatory response is generated to eliminate the invading extracellular pathogen *Trichomonas vaginalis*. However, the parasite has developed complex evolutionary mechanisms to evade the host immune response through cysteine proteases, phenotypic variation, and molecular mimicry. The purinergic system constitutes a signaling cellular net where nucleotides and nucleosides, enzymes, purinoceptors and transporters are involved in almost all cells and tissues signaling pathways, especially in central and autonomic nervous systems, endocrine, respiratory, cardiac, reproductive, and immune systems, during physiological as well as pathological processes. The involvement of the purinergic system in *T. vaginalis* biology and infection has been demonstrated and this review highlights the participation of this signaling pathway in the parasite immune evasion strategies.

Human trichomoniasis is the most common non-viral sexually transmitted infection caused by the parasite *Trichomonas vaginalis* with an incidence of 276 million new cases each year [1]. The vaginal squamous epithelium is the primary site of infection, although the parasite may also reach urethra and endocervix [2,3]. In men, the parasite leads to urethra infection and the presence of trophozoites in the prostate gland has been demonstrated [2,4]. Updated data revealed that approximately 80% of *T. vaginalis* infections are asymptomatic in both men and women [5–7].

In symptomatic women, the clinical manifestations are vaginal discharge, pruritus, odor, and irritation [3]. The typical vaginal discharge is caused due to intense leukocytic infiltration within the genital tract mainly promoted as consequence of epithelial cell death mediated by inflammation and recruitment of polymorphonuclear leukocytes [8]. In contrast

* *Corresponding author*. Parasitology Research Laboratory, Pharmacy Faculty, Federal University of Rio Grande do Sul, Ipiranga Avenue, 2752, 90610-000, Porto Alegre, Rio Grande do Sul, Brazil. Tel.: +55 5133085325; fax: +55 5133085437.
E-mail address: tiana.tasca@ufrgs.br (T. Tasca).
Peer review under responsibility of Chang Gung University.
http://dx.doi.org/10.1016/j.bj.2016.06.007

to women, the infection in men is in general self-limited, which seems to be associated to the characteristics of male genital fluid enriched in zinc that displays a critical cytotoxic effect [9]. If present, men urethritis is associated with discharge, dysuria, and mild pruritus or burning sensation immediately after sexual intercourse [10].

Studies support that the impact of trichomoniasis is not restrict to vaginal or urethral site infection but also presents a major influence in HIV transmission and acquisition [11,12], in the risk of cervical [13] and prostate cancer [14–16] and is also related to adverse pregnancy outcomes [17,18] and female and male infertility [9,19]. Despite all serious consequences attributed to the *T. vaginalis* infection the treatment is still restrict to a single therapeutic option, the nitroimidazole drug family, mainly represented by metronidazole and tinidazole. Besides the problematic associated to side effects, lack of treatment of sexual partners, inaccurate diagnosis, the increasing number of drug resistance in clinical isolates is relevant [10,20,21]. It has become clear that the impact of trichomoniasis on public health demands early and correct diagnosis, prompt treatment and constant studies on pathogenic mechanisms and host immune response involved in the infection.

The purinergic system constitutes a signaling cellular net that employs purines and pyrimidines as effectors compounds, which may be inactivated by enzymes named ectonucleotidases or uptake by cells through transporters or they can bind to purinoceptors [22]. The purinergic system is involved in almost all cells and tissues signaling pathways, especially in central and autonomic nervous systems, endocrine, respiratory, cardiac, reproductive and immune systems, during physiological as well as pathological processes [23].

In this context, the aim of this review was to highlight the immunological aspects involved in *T. vaginalis* infection, with focus on the purinergic signaling involvement in the parasite immune response evasion mechanisms.

Innate immunity

The female reproductive tract is a particular immunological site that plays a pivotal role on mucosa protection from a variety of pathogens. Besides this crucial function, the mucosal immune system of the female genital tract is in constant adaptation in order to respond to the many physiological processes that take place at this site. Hormone modulation, conception, pregnancy and protection against pathogens are some events that constantly modulate innate and adaptive responses at mucosal level [24]. In comparison with female tract, less information is available regarding the immune system in male urogenital tract, especially due to limitation on sample availability, as impermeable stratified squamous epithelium of the penile urethra difficult the collection [25]. In this sense, it is increasing the number of immunological studies in epithelial cell lines or alternative samples aiming to characterize innate and adaptive immune responses in male reproductive tract.

A distinguishing aspect of the male and female genital tract is the both immune responses activated at these sites: systemic immunity and mucosal immune reaction [24]. The immune responses in the reproductive tract are mediated by interactions between cells, anatomic components and molecules that constitutes the complex microenvironment regulated by sex hormones and specific microbiome [26,27]. Regardless of the site, the development of a multiplicity of immunological mechanisms allowed the host to prevent establishment or dissemination of pathogenic infections.

Barrier protection: epithelial cells, mucus, pH

The epithelial cells and mucus present in the female reproductive tract provide a strong physical barrier that prevent the transmission of microorganisms and specially, sexually transmitted infections [28]. The luminal portion of female reproductive tract is composed of columnar epithelial cells closely connected with tight junctions whose integrity is maintained by many factors as hormones and chemokines [26,29]. In the male reproductive tract, the urethral mucosa and the testes are responsible for immune responses in consequence of cytokines autocrine and paracrine release [30].

Integrating the physical barrier that prevents the pathogen's entry into the female and male reproductive tract, the mucus layer comprises a dense gel phase capable of trapping invasive microorganisms. Mucin family consists of glycosylated proteins that are present and expressed specifically at the apical surface of epithelial cells through genital tract [31,32]. Beyond those features, cervico-vaginal mucus may prevent the transmission of many pathogens because of the low pH, maintained by lactic acid produced by commensal bacteria, mainly *Lactobacillus* spp., in normal reproductive cycle of healthy women [33]. It was demonstrated that an increase in the vaginal pH and anaerobic bacteria are used for the clinical diagnosis of infections including bacterial vaginosis caused by *Gardnerella vaginalis* (pH > 4.5) and the parasite *T. vaginalis* (pH 5.0–6.0) [34]. The cellular and physiological constitution of female reproductive tract, including these complex components dynamically controls the initial process of establishing pathogen infection.

T. vaginalis infection: overcoming the barriers from epithelial cells and strategies of immune response evasion

As an extracellular pathogen, *T. vaginalis* infects the epithelial layer of human reproductive tract and for the success of the colonization and survival of the trophozoites the parasite must adhere to epithelial cells. The host environment is constantly changing because of diverse biological processes and the parasite needs to evade a series of non-specific host defenses, including mucus, the structure of epithelial layer, pH at the genital site, presence of chemokines and another soluble factors.

T. vaginalis is able to traverse the mucus layer first by mucin binding followed by its proteolytic degradation [35]. It was demonstrated that the parasite binds to mucin possibly by a lectin-like adhesion and proteinase action is activated [35]. The continued release of these proteins may contribute to desquamation of epithelial cells, leading to the destruction of monolayers and allowing the penetrance of the parasite [36].