Review Article

*Trichomonas vaginalis* Pathogenesis: a Narrative Review

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Abstract

In the latest articles which were published during 2013-2014, *Trichomonas vaginalis* (*T. vaginalis*) was mentioned as a neglected sexual transmission disease (STD), while the exact mechanism of its pathogenesis has not been cleared yet. Although trichomoniasis is easy curable, there is concern that resistance to drug are increasing. This common infection as concerning the important public health implications needs more research to be done for understanding the diagnosis, treatment, immunology and pathogenesis. In this review we searched all valuable and relevant information considering the pathogenesis of *T. vaginalis*. We referred to the information databases of Medline, PubMed, Scopus and Google scholar. The used keywords were the combinations of *T. vaginalis* and words associated with pathogenicity. This review discusses the host-parasite interaction and pathogenicity of this parasite.

Keywords: *Trichomonas vaginalis*, Pathogenesis, STD

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Introduction

One of the most common neglected sexually transmitted disease worldwide is trichomoniasis, which *Trichomonas vaginalis* (*T. vaginalis*), a flagellated protozoan parasite, is the causative agent but still many of pathogenicity mechanisms are unclear.1,2 *Trichomonas vaginalis* is one of the human urogenital-vaginal tract parasites, which is more common in women rather than men.3 *T. vaginalis* is typically pyriform shape parasite, although amoeboid shapes are evident in adhering stage to vaginal tissue in vivo.4 Non-dividing parasite has four anterior flagella and the size is about 7-9µm. Furthermore, the parasite has undulating membrane; one recurrent flagellum and the costa originate in the kinetosomal complex.5,6 The only natural host of this parasite is humans.7,8 This infection accounts for almost half of all curable infections worldwide.9 Trichomoniasis is frequently seen concomitantly with other sexual transmission diseases (STDs) such as gonorrhea.10 The majority of women also have bacterial vaginosis with trichomoniasis.11-13 Trichomoniasis has wide range of symptom from asymptomatic infection to severe vaginitis, which is show, a complicated relation between parasite and host.14 Symptomatic form of the disease is seen more in women rather than men. One of the reasons that led to researchers focused more on this disease during decade is to prove the patient with trichomoniasis have more risk for human immunodeficiency virus HIV infection and cervical cancer.15 All clinical isolates of *T. vaginalis* appear to be capable of infection and disease production.16 This review discusses the host-
parasite interaction, pathogenicity and vaccination of this parasite infection.

**Methodology and search strategy**

We searched all relevant information considering the association between *T. vaginalis* and pathogenesis. We referred to the information databases of Medline, PubMed, Scopus and Google scholar and the used keywords were the combinations of *T. vaginalis* and pathogenesis.

**Pathogenesis Factors**

Although *T. vaginalis* is the most common STD parasite, its pathogenesis aspects are not fully understood. New research on the early events of infection is localized. *Trichomonas* lives on the surface of epithelial cells in urinary tract and this environment provides a parasite of nutrients needed. The researchers gave different results in the two areas of work: the microscopic studies and biomedical analysis to obtain the behaviors and interactions between host and parasite. Studies on the pathogenicity of this parasite have two perspectives: Contact dependent and non-contact dependent. But many common factors between these two views are presented. Contact-dependent mechanisms include adherence and adhesions, hemolysis, enzymatic secretion and interaction with the vaginal Flora. Mechanisms of non-contact hemolysis and proteinases addition; Cell detaching factor (CDF), which is perhaps one of the most crucial factors related to contact dependent.

**Adhesion and Adhesions**

Adhesion of *T. vaginalis* to the host cell is the first and critical step in the pathogenesis of trichomoniasis. T. vaginalis undulating membrane binds to epithelial cell. It was observed that opposite side of the *Trichomonas vaginalis* undulating membrane binds to epithelial cell. Also in this area are more microfilament focused. The next molecules involved in adhesion laminin-binding proteins are located across Trichomonas. Lamin is a glycoprotein that thought to play an important role in formation, differentiation, mobility and increase adhesion ability. The increased adhesion to the basement membrane, which leads to binding to laminin here, there's probably a Chemotactic properties.

Another molecule, which has function in adhesion in *T. vaginalis*, is extracellular matrix adhesion glycoprotein ‘Fibronectin’ which probably was used in both adhesion and nutrient acquisition. The last molecules, which seem to collaborate in adhesion, are surface saccharides of host cell that have function in erythrocytes hemolysis.

Here it should be noted that the adhesive molecules which mentioned above have not associated with the virulence of the parasite, while the virulent strains isolated from patients with symptom showed wide differences in their adhesion. This is indicative of the complex relationship between host and parasite.

At the end, it should be mentioned that the knowledge about the host cell receptors which parasite adhesion molecules bind is little, however there is some evidence that laminin may be a target for trichomonad...
adhesion$^{48}$.  

**Hemolysis**

Since *Trichomonas vaginalis* is not able to synthesize iron and fatty acid for their survival individually, so it seems that RBC is one of the main sources$^{49}$. Evidences suggested that perforin like protein may be involved. Perforin like protein is kind of CP, which help to parasite for RBC hemolysis. It has been observed that CP inhibitors greatly reduce RBC lysis. But in addition, phagocytosis in another way, which help to parasite to lysis RBC. It seems that hemolytic activity of parasite has correlation with virulence.

In summary, the phenomenon of hemolysis begins by ligand receptor relationship and by using Perforin like Protein, perforated RBC wall and finally separated from RBC and RBC has become lysis$^{50-52}$.  

**Enzymatic Secretion**

Next mechanism is enzymatic secretions which CP activities have an important role in the pathogenesis of parasite. CPs have a role in nutrition, hemolysis and also help to parasite invasion.

*Trichomonas vaginalis* has 11-23 different CP activities that this enzyme has main role in parasite pathogenicity and hemolysis. In addition, CP involve as a lytic agent in RBC hemolysis$^{53-62}$. In a study which has done on CP4, gene encoding CP4 protein was cloned and expressed. In this study it has been found that antibody against CP4 prevents hemolysis of erythrocyte. This is the confirmation about key role of CP4 in RBC lysis$^{53}$. Another CP is CP30, which can cause apoptosis inducing in host cell$^{50}$.  

Next factor is *T. vaginalis* macrophage migration inhibitory factor (TvMIF), which is kind of proinflammatory cytokine, approximately 50% similar to human migration inhibitory factor (HuMIF). The evidences show that this factor is increased in prostate cancer and HuMIF play key role in the initiation and progression of cancer$^{64}$.  

In addition, CPs in *T. vaginalis* have the ability to decrease vaginal immunoglobulin G and A which will be more discussed in immune system evasion section$^{65,66}$. These proteins of *T. vaginalis* and in vivo experiments have presented that these proteins are immunogenic and could be candidate as vaccine or diagnostic tests.

**Contact-independent mechanisms of pathogenicity**

Contact-independent mechanisms which are also involved in pathogenesis mainly related to cell free filtrates (Cell Detaching Factor) which released by *T. vaginalis* itself since *Pentatrichomonas hominis*, a nonpathogenic species doesn’t have CDF activity$^{67,68}$. It has been reported that CDF which has a cytopathic effects in cell culture$^{24,69}$. CDF is a kind of glycoprotein and extracellular factor which was found to be a 200 kDa. It seems that the level of CDF probably has relationship with virulence of this disease. It also, local antibody in vaginal environment which produce by B-Cell is reduced the effect of CDF. In addition, for example hemolysis and cytotoxicity mechanisms cannot be explained by contact dependent individually, while these effects can be seen in the absence of cell to cell contact$^{70,71}$.  

**Interaction with the vaginal flora**

Another important issue in the pathogenicity can be mentioned, is interaction between *T. vaginalis* and the vaginal flora. As previously mentioned, normal vaginal pH is acidic while the optimum pH for this organism is around 5-6$^{72}$. *Trichomonas vaginalis* for restoring in vagina should be passing and overcoming vaginal cell natural barrier. One of the most important factors is the presence of lactobacilli. Phukan et al, has reported that lactobacilli caused inhibition of *T. vaginalis* adhesion with varying degrees. So *T. vaginalis* overcomes flora bacterial in the vagina by following methods$^{73}$. It has been observed that *T. vaginalis* phagocytizes bacteria, and it may accurse for lactobacilli too. Another way is cell free filtrates (CDF) or proteins, which are secreted by parasite, could be eliminating the lactobacilli$^{74}$.  

**Immune System Evasion**
The ability of parasite to evade the host immune system is one of important aspect of pathogenesis. Location is the first strategic tactics in T. vaginalis to evade the immune system which is deficient in complement. Surprisingly cervical mucus is deficient in complement which is allowed to parasite to evade complement-mediated destruction. The existing low level of complement is disappeared by the parasite’s protease secretion. Consequence of increasing the level of Iron are CP increasing and RBS lysis so environment’s iron would be increase and the expression of CP was increased as well.

Another evasion way is phenotypic variation mechanism which detect by expression or non-expression of 270kDa protein. T. vaginalis are described as positive or negative P270. T. vaginalis which is positive cannot express protein hence doesn’t have the ability of adhesion.

**Trichomoniasis in men**

The prevalence of this disease in male are less than female and most of the time appears asymptomatic, but it has been reported as an important Couse of non-gonococcal urethritis. In half of the men urethritis appears with trichomonas as the sole urethral pathogen. There is a little information of its significant in male genital tract but new researches also show a related of trichomniasis and prostate cancer.

In Seo study shows that T. vaginalis may increase IL-1β expression in human prostate epithelium through activation of ROS, ERK, and NF-kB, and this in turn may induce the migration of monocytes and neutrophils and lead to an inflammatory response. This research was confirmed inflammatory reaction caused by T. vaginalis in prostate epithelial cell.

**Conclusion**

Trichomoniasis is not merely a nuisance disease of women. It is an unpleasant, irritating, and potentially dangerous disease that can go undiagnosed for years and is often passed on by an asymptomatic carrier. It is the world’s most common nonviral STD, and it is strongly associated with several complications in pregnancy and with an increase in the transmission of HIV.

T. vaginalis is a very complex organism, from its biochemistry to the mechanisms of pathogenesis. Areas of pathogenesis that should be pursued include defining soluble factors, further elucidating the contact-dependent relationship between the vaginal epithelium and T. vaginalis, and defining how the organism can establish itself in a normally inhospitable and changing environment. It will also be important to further define the role of the human immune system in trichomniasis in order to develop targeted intervention strategies. With continued collaboration and cooperation within the scientific community, we may one day understand the pathogenesis of T. vaginalis well enough to develop a safe, effective, and cost-effective vaccine.

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